DISSERTATION ON

ETIOLOGY, CLINICAL PROFILE AND OUTCOME OF HEMIPLEGIA IN CHILDREN AGED 2 MONTHS TO 12 YEARS

Dissertation submitted to

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MADRAS MEDICAL COLLEGE

CHENNAI

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CERTIFICATE

Certified that this dissertation entitled **"Etiology, Clinical Profile and Outcome Of Hemiplegia In Children Aged 2 Months To 12 Years"** is a bonafide work done by **Dr. A. Mohana Geetha, M.D.,** Post graduate, Institute of Child Health and Hospital for Children, Madras Medical College, Chennai, during the academic year 2006-2009.

Prof.P.RAMACHANDRAN,
M.D.,D.N.B.,
Chief MV Unit
Institute of Child Health
and Hospital for Children,
Madras Medical College,
Chennai.

Prof. N. THILOTHAMAL
M.D.D.M., Neuro
Professor of Neurology,
Institute of Child Health
and Hospital for Children,
Madras Medical College,
Chennai.

Prof. SARADHA SURESH,
M.D.,Ph.d.,F.R.C.P.(Glasgow),
Director and Superintendent,
Institute of Child Health
and Hospital for Children
HOD and Professor of Paediatrics,
Madras Medical College,
Madras Medical College,
Chennai.

Prof. T. P. KALANITHI, M.D.,
Dean,
Madras Medical College,
Chennai.

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CONTENTS

INTRODUCTION

Hemiplegia secondary to vascular disorders occurs in children with an incidence of about 1 – 3 cases per 1,00,000 per year. The pediatric causes of stroke are distinctive compared with adult causes. ~~The causes of stroke in children are far different from the usual causes in adults.~~ Children have not had the time to develop hardening of the arteries (atherosclerosis) or other long-term effects of hypertension, high cholesterol, diabetes, and smoking that are among the most common stroke risks in adults.

As with adults, the functional deficits caused by the stroke depend on its size and the specific areas of the brain affected. Paralysis of affected limbs and subsequent development of spasticity in those limbs can occur if motor areas are affected. Balance mechanisms are impaired if the cerebellum or its related structures are involved. Language deficits (aphasia) occur if language areas are involved. The list is as long as that for adults. Children, however, have more "plasticity" in their brains, meaning ~~. This means~~ that the areas of the brain have not yet been "locked" into their lifelong function. Thus other areas of the brain can take over the function of destroyed parts to a somewhat greater degree than in adults. The result is that children with stroke tend to have a greater degree of recovery in the long term than adults do. The younger the child at the time of stroke, the greater is this tendency. ~~arterial thrombosis,~~ In children the relative rarity of the condition contributes to the reluctance in ~~to~~ considering the diagnosis.

NIoCH, Chennai

ARTERIAL SUPNEUROANATOMY

PLY OF THE BRAIN

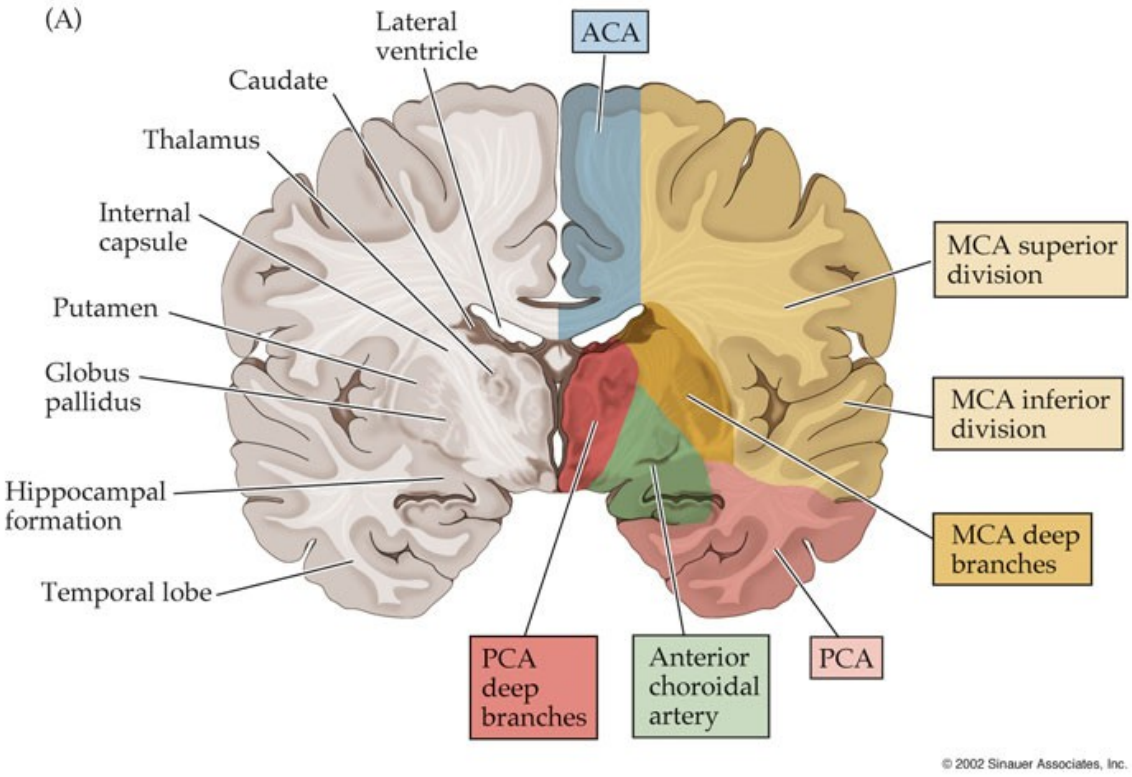
Characteristics of the Cerebral Arteries

The CIRCLE OF WILLIS

It is is a confluence (actually a hexagon) of vessels that gives rise to all of the major cerebral arteries. It is fed by the paired internal carotid arteries and the basilar artery. When the circle is complete, it contains a posterior communicating artery on each side and an anterior communicating artery. Despite these variations, occlusion of each of the major cerebral arteries usually produces a characteristic clinical picture.

The arteries course in the subarachnoid space, often for a considerable distance, before entering the brain itself; rupture of an aneurysm of of a vessel (eg, from an aneurysm that has burst) tends to cause a subarachnoid hemorrhage.

Each major artery supplies a certain territory, separated by **border zones (watershed areas)** from other territories; sudden occlusion in a vessel affects its territory immediately, sometimes irreversibly.



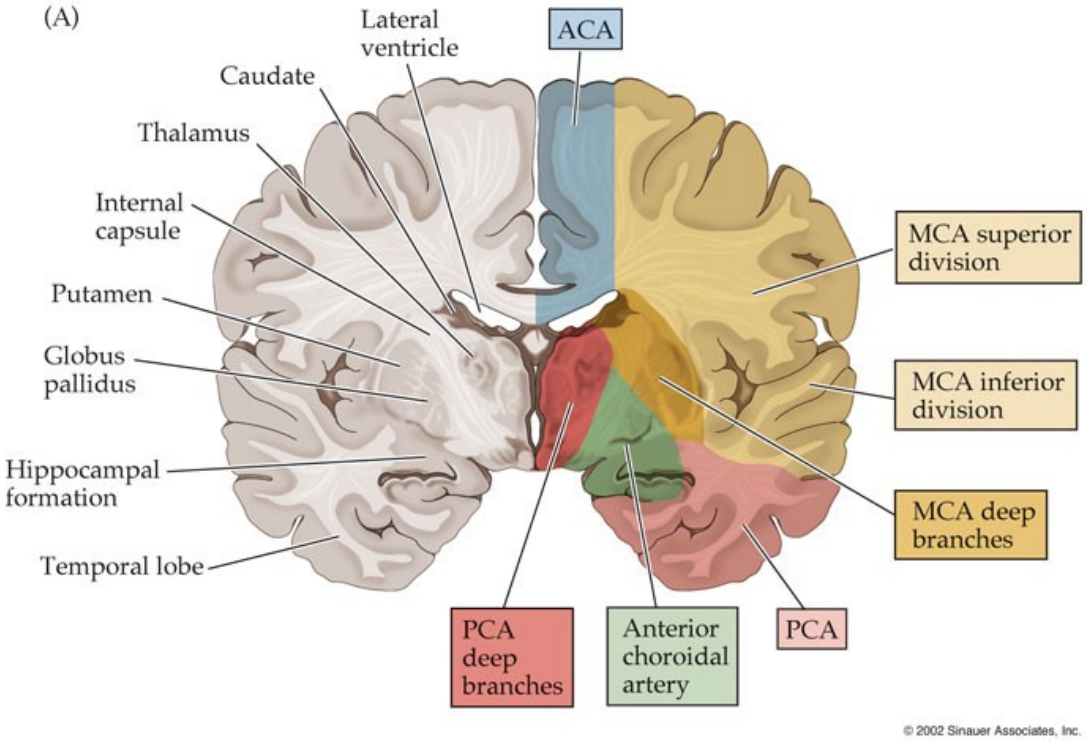
PRINCIPAL ARTERIES

The arterial blood for the brain enters the cranial cavity by way of two pairs of large

vessels): the **internal carotid arteries,** which branch off the common carotids, and the **vertebral arteries,** which arise from the subclavian arteries. The vertebral arterial system supplies the brain stem, cerebellum, occipital lobe, and parts of the thalamus, and the carotids normally supply the remainder of the forebrain (Fig. 1). ~~The carotids are interconnected via the **anterior cerebral arteries** and the **anterior communicating artery;** the carotids are also connected to the **posterior cerebral arteries** of the vertebral system by way of two **posterior communicating arteries,** part of the circle of Willis~~

Abbreviations ~~bbr~~	Name of Artery	Distribution
ACA	Anterior Cerebral Artery	Supplies most medial portions of frontal lobes and superior medial parietal lobes
AComA	Anterior Communicating Artery	Connects the anterior cerebral arteries at their closest juncture
ICA	Internal Carotid Artery	Ascends through base of skull to give rise to the anterior and middle cerebral arteries, and connect with posterior half of circle of Willis via posterior communicating artery
MCA	Middle Cerebral Artery	Trifurcates into temporal, frontal, and parietal branches that supply most of the parenchyma of these lobes
PComA	Posterior Communicating Artery	Connects the anterior circle of Willis with the posterior cerebral artery of vertebral-basilar circulation posteriorly
PCA	Posterior Cerebral Artery	Supplies the occipital lobe and the inferior portion of temporal lobe. A branch supplies the choroid plexus.
SCA	Superior Cerebellar Artery	Supplies the dorsal cerebellum, pons, and midbrain
BA	Basilar Artery	Formed by the junction of the two vertebral arteries, it terminates as a bifurcation into the posterior cerebral arteries
AICA	Anterior Inferior Cerebellar Artery	Supplies the inferior cerebellum and portions of pons and medulla
VA	Vertebral Artery	The vertebrals emerge from the posterior base of skull and merge to form the basilar artery
PICA	Posterior Inferior	Supplies the inferior-posterior cerebellum,

Abbreviations ~~bbr~~	Name of Artery	Distribution
	Cerebellar Artery	choroid plexus in 4th ventricle, and portions of medulla
ASA	Anterior Spinal Artery	Descends along the anterior (ventral) aspect of the spinal cord


(A)
Lateral ventricle
ACA
Caudate
Thalamus
Internal capsule
MCA superior division
Putamen
Globus pallidus
MCA inferior division
MCA deep branches
Hippocampal formation
Temporal lobe
PCA deep branches
Anterior choroidal artery
PCA
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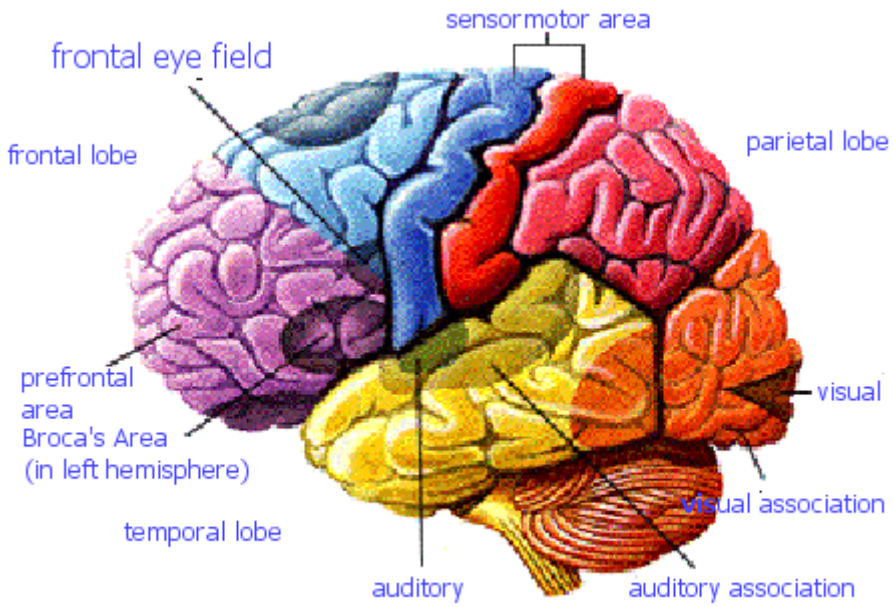
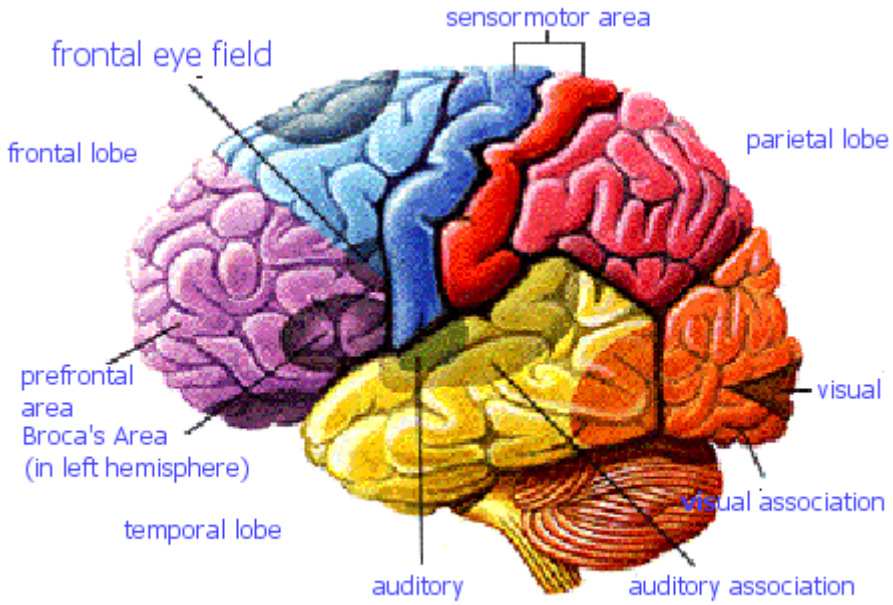

sensormotor area
frontal eye field
frontal lobe
parietal lobe
prefrontal area
Broca's Area
(in left hemisphere)
visual
visual association
temporal lobe
auditory
auditory association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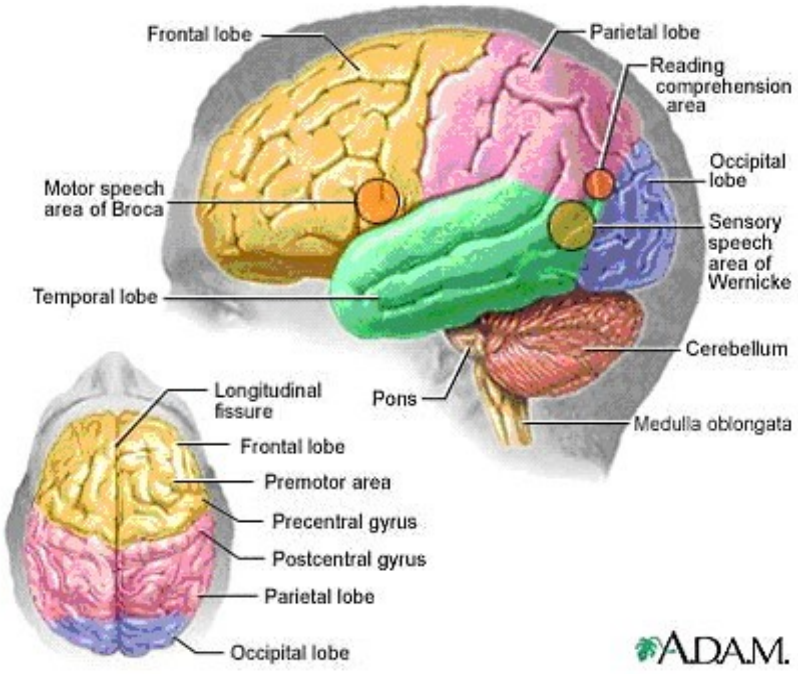
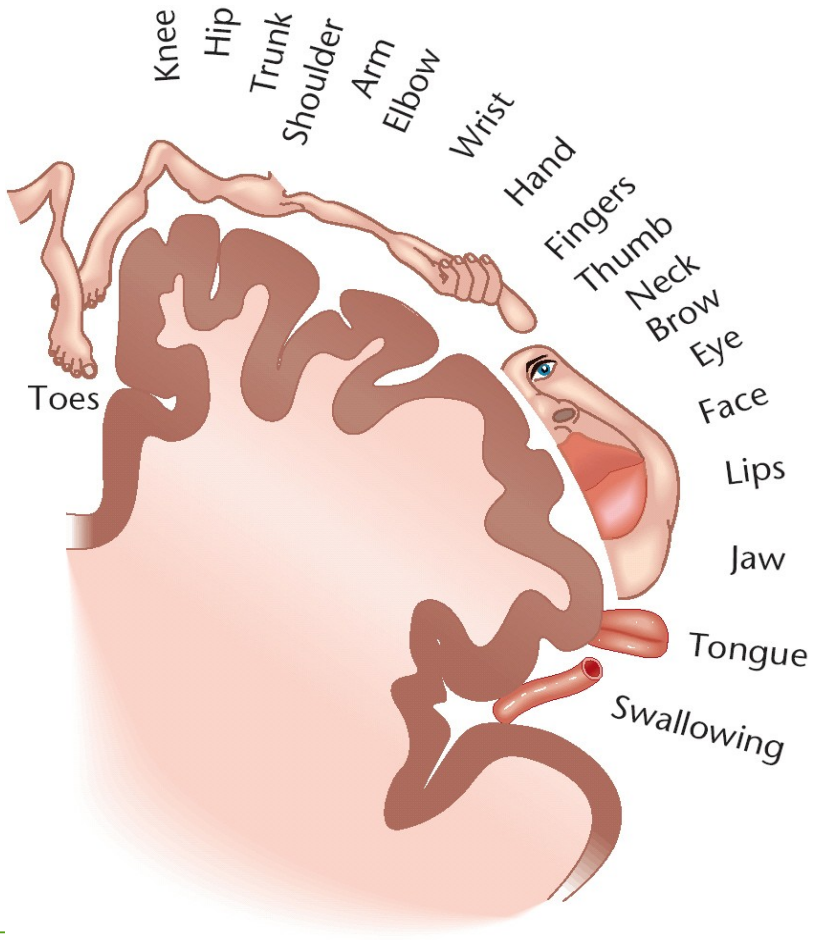
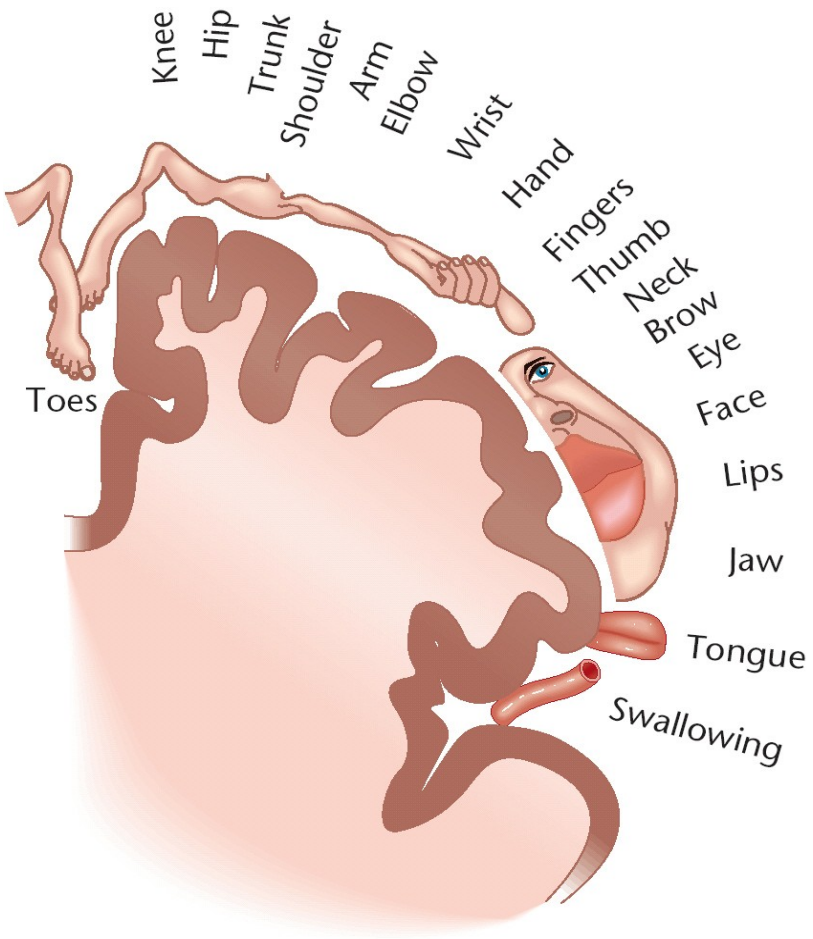

Frontal lobe
Parietal lobe
Reading comprehension area
Occipital lobe
Motor speech area of Broca
Sensory speech area of Wernicke
Temporal lobe
Cerebellum
Pons
Medulla oblongata
Longitudinal fissure
Frontal lobe
Premotor area
Precentral gyrus
Postcentral gyrus
Parietal lobe
Occipital lobe
A.D.A.M.

MOTOR HOMUNCULUS

A figurative representation of the body map encoded in primary motor cortex. Body parts with complex repertories of fine movement, like the hand, require more cortical space in M1, while body parts with relatively simpler movements, like the hip, require less cortical space. (Fig. 2).


Knee
Hip
Trunk
Shoulder
Arm
Elbow
Wrist
Hand
Fingers
Thumb
Neck
Brow
Eye
Face
Lips
Jaw
Tongue
Swallowing
Toes



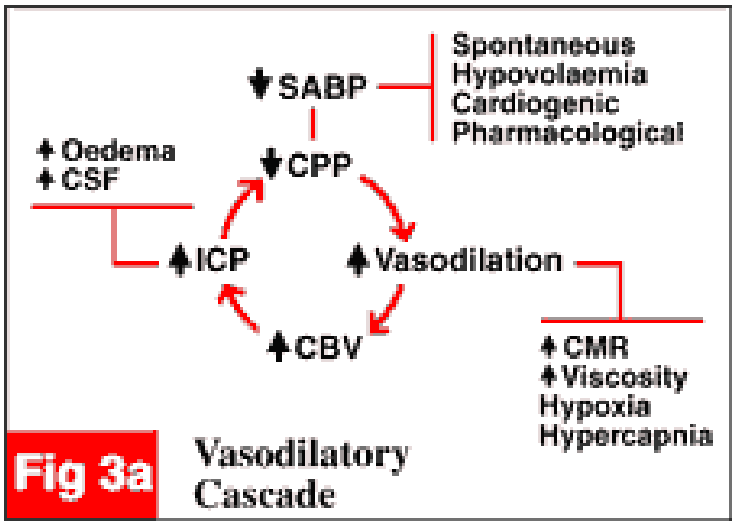
PATHOPHYSIOLOGY

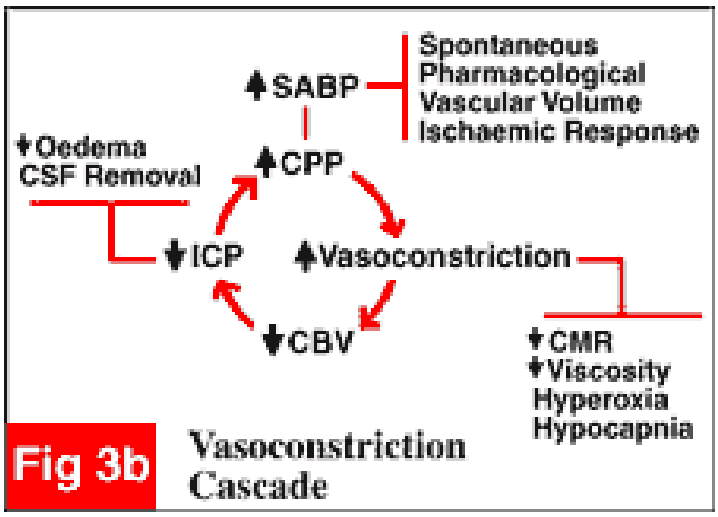
~~-size~~//~~'~~//~~100g/min~~Cerebral Perfusion Pressure

Cerebral perfusion pressure (CPP) is defined as the difference between mean arterial and intracranial pressures. Normal cerebral perfusion pressure is 80 mmHg, but when reduced to less than 50 mmHg there is metabolic evidence of ischemia and reduced electrical activity. Mean arterial pressure is the diastolic pressure plus one third of the pulse pressure (difference between the systolic and diastolic).

CPP = MAP – ICP

Cerebral blood flow is maintained at a constant level, ranging from 20ml/100g/min in white matter to 70ml/100g/min in grey matter, in the face of the usual fluctuations in blood pressure by the process of autoregulation. –**Autoregulation** maintains a constant blood flow between MAP 50 mmHg and 150 mmHg. However in ~~traumatised~~traumatized or ~~ischaemic~~ischemic brain~~,~~ CBF may become blood pressure dependent. Thus as arterial pressure rises so CBF will rise causing an increase in cerebral volume. Similarly, as pressure falls, ~~so~~ CBF will also fall, reducing ICP, but also inducing an uncontrolled reduction in CBF. In this situation if CPP falls below the critical value of 70 mmHg, the patient will have inadequate cerebral perfusion. Autoregulation will cause cerebral vasodilatation leading to a rise in brain volume. This in turn will lead to a further rise in ICP and induce the vicious circle described by the vasodilatation cascade (Fig 3a) which results in cerebral ischaemia. This process can only be broken by increasing the blood pressure to raise CPP, inducing the vasoconstriction cascade (Fig 3b). **Carbon dioxide** causes cerebral vasodilation, whereas **Oxygen**~~.~~ ~~:~~causes cerebral vasoconstriction.





ISCHEMIC PENUMBRA

Core is the central area where ischemia is severe & infarction develops rapidly with a blood supply of 0 – 12 mL/100 g/min.

Penumbra ~~**(fig 6)**~~ is the marginally perfused area surrounding the core which has the capacity to recover should perfusion be restored promptly with a blood supply of 20–50 mL/ 100 g/ min.

Complete interruption of cerebral blood flow results in

- Suppression of electrical activity within 12– 15 sec
- Inhibition of transsynaptic excitation after 2- 4 min
- Inhibition of electrical excitability after 4- 6 min
- Breakdown of metabolism shortly thereafter

Neurons and glia remain alive but functionless for as long as 30 min before cellular death occurs. The possibility that restoration of flow during the interval between loss of neuron activity and tissue death might restore function is the basis for therapy of the evolving cerebral infarction (Fig. 4)..

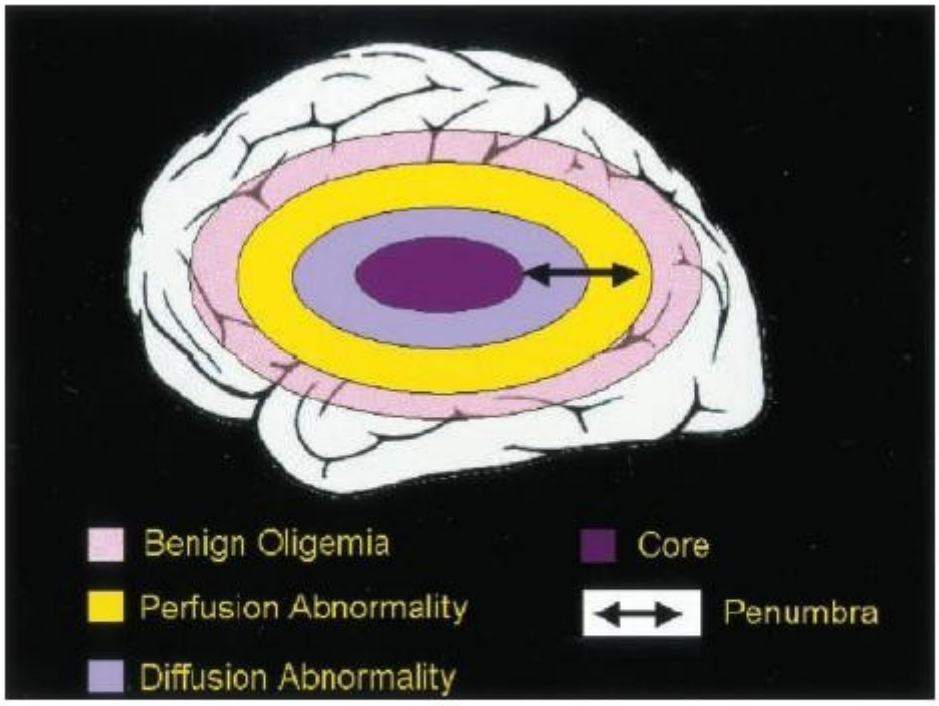


Figure 6. Modified view of MRI-defined ischemic penumbra in which the penumbra equals not only regions of diffusion-perfusion mismatch but also a portion of the diffusion abnormality itself.

DEFINITION ANSD CAUSES OF HEMIPLEGIA:

DEFINITION

Hemiplegia is defined ais a condition involving total ~~paralysis~~ or partial paralysis of one side of the body.

~~MOTOR HOMUNCULUS~~

~~A figurative representation of the body map encoded in primary motor cortex.~~

~~Body parts with complex repertories of fine movement, like the hand, require more cortical space in M1, while body parts with relatively simpler movements, like the hip, require less cortical space.~~

CAUSES OF HEMIPLEGIA

The differential diagnosis of acute hemiplegia includes more than stroke. At least three other disorders need to be considered in children.

- Transient postictal hemiparesis (Todd paralysis) lasts less than 24 hours, usually has epileptiform activity on EEG ~~,~~and never has acute infarction on MR imaging.

- Complicated migraine is usually preceded by severe headache; focal deficits usually last hours, rarely up to a week; often there is a family history of migraine or specifically hemiplegic migraine ~~;~~and MR or neuroimaging studies are normal.

- Alternating hemiplegia is a rare disorder of unknown etiology. It usually begins in children younger than 2 years; episodes of hemiplegia last minutes to hours, rarely longer than a day; weakness varies between sides; seizures are common but usually do not occur during episodic weakness; and most children have a progressive neurodevelopmental deterioration.

STROKE

A clinical syndrome typified by rapidly developing signs of focal or global disturbance of cerebral functions, lasting more than 24 hours or leading to death, with no apparent causes other than of vascular origin.

~~Stroke is defined as the sudden occlusion or rupture of cerebral arteries or veins resulting in focal cerebral damage and clinical neurologic deficits that persist for longer than 24 hours.~~

TYPES OF STROKES:

~~Stroke can be ischemic, hemorrhagic, or both.~~

Ischemic stroke can be either arterial or venous.

Arterial strokes usually result from thromboembolic occlusion of cerebral arteries.

Venous strokes result from thrombosis in cerebral veins and sinuses.

Hemorrhagic stroke can occur from bleeding into an acute ischemic stroke or from rupture of intracranial arteries.

- ~~In children, ischemic stroke is more common than hemorrhagic stroke.~~

TIMING OF STROKES

- **Before 28 days of age:**
  - **Perinatal stroke** encompasses cerebrovascular events that occur from ~~between the~~ 28 weeks of gestation ~~and~~ to one month following birth.

- A stroke that occurs before birth may also be called an **in-utero stroke or fetal stroke**. Another term often used in this group is **prenatal stroke**. Stroke occurs more frequently in the perinatal and prenatal age group than in older children.

- **Childhood stroke** occurs between 1 month and 18 years of age.

INCIDENCE OF STROKE

Arterial ischemic stroke around the time of birth is recognized in one in 4000 full-term infants (2).

Arterial ischemic stroke which occurs in childhood ranges from 0.6 to 7.9 per 100,000 children (1).

Approximately 75% are arterial and 25% sinovenous thrombosis.

The incidence of hemorrhagic stroke in children is estimated at 1.5 to 5.1 per 100,000 children per year.

CLINICAL PRESENTATION

The most common clinical presentation of clinical stroke in childhood is acute hemiparesis.

Headache and vomiting are common in children with hemorrhagic stroke and

Headache and decreased level of consciousness in children with cerebral venous thrombosis. Seizures, facial palsy and aphasia can be associated features depending on the area involved.

~~M~~EITIOLOGY~~AJOR CAUSES~~ OF ISCHEMIC STROKE IN CHILDREN

Cardiac (25-50%)

Congenital heart disease -~~—~~

VSD, ASD, PDA, T~~t~~etralogy of Fallot, aortic stenosis, coarctation of the aorta ~~, VSD, ASD, PDA~~

Acquired heart disease -~~—~~

R~~r~~heumatic fever, prosthetic valve, endocarditis, cardiomyopathy, atrial myxoma,

~~rhabdomyoma~~

Cardiac surgery

Hematologic

Prothrombotic state (35%)

~~abnormal activated~~Activated protein C resistance (factor V Leiden)~~;~~

~~deficiencies of protein~~Protein C, protein S and ~~,~~ antithrombin III deficiencies~~,~~

~~antithrombin III;~~

P~~p~~rothrombin gene mutation~~;~~

A~~a~~ntiphospholipid antibodie~~s~~s~~;~~

L~~l~~upus anticoagulant

Sickle-cell anemia (10%)

Disseminated I~~i~~ntravascular C~~e~~oagulation

Leukemia, hemophilia, thrombocytopenia, polycythemia

Traumatic

Arterial dissection (10-25%)

Intraoral trauma

Fat or air embolism

Vascular

Moyamoya syndrome (25%)

Fibromuscular dysplasia

Migraine

Vasculitis

Meningitis - —bacterial, viral, TB, fungal, parameningeal

Varicella

Systemic Lłupus Eerythematosus

Takayasu arteritis

Kawasaki disease

Inflammatory bowel disease

Drug abuse - —cocaine, amphetamine

Metabolic

Organic acidurias

Homocystinuria

Propionic, methylmalonic, isovaleric aciduria

Glutaric aciduria (I, II)

Mitochondrial

Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes -(MELAS)

Leigh syndrome - —pyruvate dehydrogenase complex defects

Cytochrome oxidase deficiency

Lysosomal

Fabry disease

Cystinosis

Urea cycle defects

Partial ornithine transcarbamylase deficiency

Carbamyl phosphate synthetase deficiency

Other metabolic causes

Molybdenum cofactor deficiency

Sulfite oxidase deficiency

—Familial hyperlipidemia

—**Toxic**

Cocaine,

Methamphetamine,

Phencyclidine

The reported incidence varies between different centers, possibly reflecting differences in referral patterns, populations studied, and investigator expertise. Many children have multiple risk factors.

~~**STROKE IN SICKLE CELL DISEASE (SCD)**~~

Age years	Incidence, number of strokes per 100 patient years	Prevalence, %
<2	0.13	2.29
2-5	1.02	4.93
6-9	0.79	5.52
10-19	0.41	5.33

ETIOLOGY OF HEMORRHAGIC STROKE

Trauma

Shaken impact syndrome

Head trauma - —closed, penetrating, vaginal delivery

Coagulopathy

—Hemophilia

—Thrombocytopenia - —idiopathic, thrombotic, hemolytic-uremic syndrome

—Liver disease

—Neonatal vitamin K deficiency

—Anticoagulants - —warfarin, heparin

Vascular anomalies

—Arteriovenous malformation

—Cavernous malformation

—Aneurysm - —congenital, traumatic, coarctation of the aorta

Sickle-cell disease

Others

—Hypertension

—Drug abuse - —cocaine, amphetamine

—Hemorrhagic transformation of ischemic infarction

GUIDELINE FOR MANAGEMENT:

There are no published consensus guidelines on the evaluation of stroke in children, but several systematic approaches have been recommended. The evaluation should include:

- Questions about any history of head trauma, neck trauma, recent infection, illness, unexplained fever or malaise, drug ingestion, developmental delay, family history of bleeding problems, and associated headache.
- Careful family history, with special attention to premature vascular disease, hematologic disease, mental retardation.
- Physical exam including head circumference in children, skin abnormalities, cardiac evaluation and carotid artery examination.

- MRI and MRA (CT if MR unavailable).

If the MRI and MRA reveal an infarct, with vascular distribution, then consider the following diagnostic tests:

1. Echocardiogram, EKG
2. Blood studies including CBC, Protein S, Protein C, Antithrombin III, homocysteine, lipid profile, antiphospholipid antibody, infection screen
3. Tuberculosis screening
4. Lumbar puncture
5. Transcranial Doppler

If the MRI and MRA reveal an infarct, with non-vascular distribution, then consider the following diagnostic tests:

- Plasma Lactate and pyruvate

If the MRI and MRA reveal a hemorrhage, then consider the following diagnostic tests:

- Coagulation studies

If the MRA is normal, then consider the following diagnostic tests:

- Conventional Angiography

General Diagnostic Evaluation

The general approach to diagnostic evaluation should be question - and hypothesis-driven:

1.- Is there a cerebrovascular lesion? Several disorders can mimic a stroke. Transient neurologic deficits can be seen after a seizure, with hypoglycemia or complicated migraine.

2.- Is there a cerebral infarction or hemorrhage? This is crucial because etiology and treatment are different between these two processes.

3.- What is the cause of the stroke? Congenital heart disease, sickle-cell disease, and prothrombotic disorders are common. No cause can be found in about one-third of patients.

Initial evaluation includes a CBC with platelet count, electrolytes and glucose, PT/PTT, toxicology screen, chest x-ray, and ECG.

Computed cranial tomography (CT) without contrast, is usually the first imaging test used because it is easy to perform and readily available. The head CT can distinguish between hemorrhage and ischemic infarction but is often normal in the first hours of infarction sometimes up to 24 hours. A subtle effacement of sulci may be the first clue to infarction.

Magnetic resonance imaging is more sensitive than CT for early detection of infarction, but it may be normal in the first few hours.

Diffusion-weighted imaging is good for early detection of infarction and if positive can help date the stroke.

Magnetic resonance angiography is a good method to detect changes in blood flow in the large intracranial and cervical vessels but less reliable with small vessels.

Magnetic resonance venography is the investigation of choice for cerebral venous thrombosis.

Once the diagnosis of stroke is established, a comprehensive workup must be performed. **Transesophageal echocardiography (TEE)** may be more accurate than transthoracic echocardiography (TTE) to detect structural abnormalities of the heart. Bubble contrast should be used to detect right-left shunt. Because embolism is the most frequent cause of childhood stroke, a careful cardiac examination is essential.

Lumbar puncture (LP), for cerebrospinal fluid examination, should be done if infection, inflammation, or subarachnoid hemorrhage (SAH) is suspected. This procedure should not be performed if there is clinical or neuroradiologic evidence for increased intracranial pressure. LP in a patient with a unilateral hemispheric or cerebellar lesion may lead to transtentorial or transmagnal herniation. Small SAH may be evident in the cerebrospinal fluid but not on head CT.

Transcranial Doppler (TCD) is a noninvasive and portable method used for imaging the circle of Willis and the vertebrobasilar system.

TCD is useful in predicting stroke in children with sickle cell disease, and can detect vasospasm in SAH.

Evidence for **prothrombotic state, coagulopathy, systemic infection or inflammation** should be carefully investigated. Approximately 30% of children with ischemic stroke have abnormalities in their prothrombotic factors. Lactate and pyruvate levels should be obtained if mitochondrial disorder is suspected. CSF lactate and pyruvate values may be necessary to make the diagnosis, even though serum levels are normal. Hemoglobin electrophoresis; VDRL, HIV, and varicalla titers; and PPD should be done when clinically indicated.

The diagnostic evaluation should not stop if one risk factor is identified, because pediatric stroke patients can have more than one cause for their cerebrovascular event.

Conventional angiography should be reserved for patients with nontraumatic intracranial hemorrhage or when vasculitis is suspected, if other imaging modalities have been normal. Small aneurysms, arteriovenous malformation, or cavernous malformations may not show up on MR imaging or MR angiography. The angiography may not detect vascular malformations if they are surrounded by hematoma and edema. Repeating the angiography or waiting until the hematoma has resolved may be necessary in this case.

If there is no evidence for infarction or intracranial hemorrhage, other **conditions that mimic stroke** such as transient postictal hemiparesis, migraine, hypoglycemia, and alternating hemiplegia must be excluded

Summary of information provided at the CHASA medical conference, 2002.

Algorithm showing the evaluation of stroke in the pediatric patient.

~~Algorithm showing the evaluation of stroke in the pediatric patient.~~

~~CAUSES OF ISCHEMIC STROKE IN A CHILD~~

~~Risk factors for acute stroke are present in 80% of children. Even children with an obvious cause for their stroke should have a detailed workup for other associated factors.~~

~~Varicella within 9 months of the infarction suggests possible varicella vasculopathy. Oral contraceptives, amphetamines, and cocaine predispose to infarction. A family history of early-onset stroke or heart disease, pulmonary embolism, or deep vein thrombosis increases the risk of an inherited prothrombotic disorder.~~

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IDIOPATHIC: one-third of cases

CARDIAC DISORDERS OR HEART DISEASES

Complications of congenital heart disease cause more than 25% of the identifiable causes of pediatric stroke. Most of these are caused by emboli that arise in the heart or are shunted through the heart. Emboli should be suspected whenever there are multiple infarctions.

Emboli can be infectious or noninfectious.

- Septic emboli from bacterial endocarditis can cause stroke from infarction or rupture of mycotic aneurysms.

- Noninfectious emboli can be cardiogenic or systemic.

Emboli formed on the left side of the heart have direct access to the cerebral circulation.

Thrombus can form in the apex of poorly contracting ventricles.

Marantic endocarditis occurs in children with malignancies or coagulopathies.

Many emboli arise from prosthetic cardiac valves.

Cardiac rhabdomyoma in children with tuberous sclerosis can be a source of emboli.

Systemic venous emboli can reach the cerebral circulation if an atrial or ventricular septal defect permits intracardiac right-to-left shunting. Patent foramen ovale is a common finding on echocardiography. These are usually innocent, but on occasion emboli can pass through them and cause stroke. Systemic emboli can arise from venous clots in children with prothrombotic disorders.

Air emboli can occur during cardiac surgery.

Fat emboli can arise from long-bone fractures.

Up to 50% of strokes in children with congenital heart disease occur within 3 days of catheterization or surgery. The exact incidence of stroke is unknown and depends on numerous variables, including the surgical procedure performed. Recent studies report strokes in up to 8.8% of children following Fontan surgery. There is a 5% risk of stroke during valve replacement surgery when children are not anticoagulated. With anticoagulation, the risk is much lower.

Children with cyanotic heart disease and polycythemia are at risk for thrombotic stroke when decreased cardiac output lowers cerebral blood flow.

This is most common in children younger than 2 years. Strokes occur in up to 4% of children with tetralogy of Fallot or transposition of the great arteries.

BLOOD DISORDERS are the second most common cause of stroke in children. Several blood disorders associated with stroke in children include:

Coagulation disorders:

Thrombophilia means an increased tendency for the blood to clot. There are several reasons why the blood by have this increased tendency to clot and these include problems with proteins in the blood. Proteins are needed to help the blood clot. If a protein has an odd shape or there isn't enough or there's too much of a it, then there may be problems with clotting. Sometimes inherited conditions from one or both parents may cause problems with these clotting proteins. Sometimes a genetic mutation can cause thrombophilia. A person who has inherited thrombophilia is at increased risk of developing a blood clot and this blood clot can cause a stroke.

Inherited causes of thrombophilia include: deficiencies of antithrombin, protein C and protein S; elevated Factor VIII; Factor V Leiden (activated protein C resistance); Factor II 20210A; and dysfibrinogenemia. Most of these are autosomal dominantly inherited. Hyperhomocysteinemia may be inherited or acquired and non-inherited factors influence Factor VIII levels.

Tests for Hypercoagulable State: CBC, PT, PTT, Proteins C and S, Antithrombin, Factor V Leiden (and/or APC resistance), Factor VIII C, Factor II 20210 A, Fasting homocysteine, Lupus Anticoagulant, and anticardiolipin antibody.

Ischemic stroke can be caused by either inherited or acquired coagulation disorders. Approximately 30% of children with ischemic infarction have one or more abnormalities in prothrombotic factors, most frequently an anticardiolipin antibody. Stroke usually occurs in the setting of a systemic illness, other acute problem, or second risk factor that temporarily increases the risk of thrombosis.

The inherited coagulation disorders include activated protein C resistance (factor V Leiden); deficiencies of protein C, protein S, or antithrombin; prothrombin gene mutation; and hyperhomocysteinemia. Activated protein C resistance is a very common cause of venous thrombosis but rarely causes arterial thrombosis in older children and adults. The risk of thrombosis is increased in patients who smoke or use oral contraceptives. Activated protein C resistance is usually caused by a mutation in factor V, and this has been reported as a cause of neonatal stroke and hemiplegic cerebral palsy.

Deficiencies of protein C, protein S, or antithrombin occur much less frequently than activated protein C resistance. Over 250 gene mutations cause these disorders. Some of these reduce protein production; others alter protein function. Because of this, functional assays of protein C, protein S, or antithrombin are the most effective way to screen for these disorders. Any of these disorders can cause ischemic stroke in children. **Neonates with homozygous mutations can have purpura fulminans or disseminated**

intravascular coagulation. Acquired deficiencies can result from vitamin K deficiency, oral anticoagulants, oral contraceptives, nephrotic syndrome, liver disease, recent thrombosis, surgery, or disseminated intravascular coagulation.

Acquired coagulation disorders are much more common. In a prospective study of 92 children with cerebral thromboembolism, 38% of the children had a prothrombotic disorder. The vast majority of these were antiphospholipid antibodies, either anticardiolipin antibody or lupus anticoagulant. Many patients had multiple abnormal prothrombotic factors, suggesting an acquired process. The abnormalities may persist for months or may fluctuate.

The antiphospholipid antibody syndrome is characterized by a positive antiphospholipid antibody and recurrent thrombotic events. The disorder is primary if there is no systemic disease and secondary if the child has systemic lupus erythematosus. Antiphospholipid antibody syndromes are rare causes of pediatric stroke. When they occur, they need to be treated with oral anticoagulants or low-molecular-weight heparin.

Among several factors involved in the origin of pediatric stroke, the role of an inherited promthrombotic state is currently under investigation. Some researchers suggest that a detailed search for mutations in inherited thrombophilia is necessary in all cases of pediatric stroke.

Definitions

Anticardiolipin Antibodies

Antiphospholipid syndrome (APS): currently recognized as a common risk factor for arterial or venous thromboembolic disease.

Factor V Leiden is an inherited disorder that can lead to abnormal blood clotting (coagulation) or thrombophilia. The Factor V Leiden is the most common hereditary blood coagulation disorder in the United States. The name Factor V Leiden means that there's a mutation in the DNA in the gene used to make the Factor V protein.

Hyperhomocysteinaemia: elevated homocysteine plasma levels have been found in children with stroke

Methylenetetrahydrofolate Reductase Mutation (MTHFR): One of the most common genetic defects of homocysteine metabolism is a mutation in the enzyme MTHFR. Increased plasma homocysteine is a risk factor for arteriosclerotic vascular disease and deep-vein thrombosis.

Plasminogen deficiency: an uncommon cause of inherited thrombosis.

Protein C and Protein S: involved in regulation of coagulation (blood clotting); they inactivate factors V and VIII.

Protein C deficiency: can result in excessive clotting. These clots tend to form in veins, not arteries. This disorder can be either inherited or acquired

Protein S deficiency: can result in excessive clotting tendencies. These are usually vein clots, such as deep vein thrombosis, but occasionally this disorder can be associated with arterial clots

Prothrombin Gene mutation 020210: an inherited mutation that can result in blood clots. A mutation in the prothrombin gene makes the body produce too much of the prothrombin protein, resulting in an increased tendency for the blood to clot.

Sickle cell anemia

Approximately 10% of pediatric strokes occur in children with sickle-cell disease (SCD). Children with SCD can have TIAs, ischemic stroke, hemorrhagic stroke, or any combination of these. As a rule, ischemic stroke occurs most frequently in infants and young children, and hemorrhagic stroke occurs in adults. The incidence of stroke is highest in children with the SS genotype, but other common genotypes (SC, S-β^+, S-β^0) also have an increased risk.

The risk of stroke varies widely in different reports. The results of the Cooperative Study of Sickle Cell Disease are summarized in Table 25-14. Stroke rarely occurs in children younger than 2 years. Children between 2 and 5 years have the highest incidence. The overall prevalence in children younger than 20 years was 5.5%.

Factors that increase the risk of ischemic stroke include prior transient ischemic attacks (TIAs), low hemoglobin concentration, acute chest syndrome, and increased blood pressure. Children with SCD and α-thalassemia have a lower

risk of stroke, possibly because they have a higher hemoglobin concentration. Although a high concentration of hemoglobin F decreases the risk of other complications of SCD, it does not lower the risk of stroke.

As many as 17% of children with SCD have radiographic evidence of stroke but do not have a history of stroke or TIA. "Silent infarctions" may cause lower IQ scores in children without obvious neurologic disease. Children with silent infarctions have an increased risk of symptomatic stroke and require very close surveillance.

Most ischemic strokes result from occlusion of large cerebral vessels, but small vessels can also be involved. Strokes often occur during a sickle-cell crisis. If narcotic analgesics are used for a painful crisis, the symptoms of stroke may be difficult to interpret. Most children present with hemiparesis, but aphasia, ataxia, visual disturbances, and seizures can also occur. Neurologic recovery depends on the size and location of the stroke. Most children regain motor function, but language deficits may persist. Ischemic stroke is rarely fatal, but there is a 26% mortality rate after hemorrhagic stroke.

Recurrent strokes are a major problem in children with SCD. Without treatment, 50 to 65% of children with one stroke will have a second. The vast majority of second strokes occur within 3 years of the first stroke.

Ischemic stroke is best visualized with MR imaging. Smaller lesions can be detected with MR than with CT imaging. In addition, stroke can be detected earlier with MR imaging, especially if diffusion-weighted sequences are

obtained. Magnetic resonance angiography (MRA) may reveal an isolated abnormality but more commonly shows a widespread vasculopathy.

The incidence of recurrent stroke can be reduced significantly with chronic transfusions to maintain the hemoglobin S concentration below 20 to 30%. Children treated with frequent transfusions have a high incidence of alloimmunization and iron overload. Vascular abnormalities may improve with chronic transfusions. Strokes may recur when transfusions are stopped; therefore most centers continue transfusion therapy indefinitely.

Children at risk for first stroke can be detected with transcranial Doppler ultrasonography (TCD). Patients with mean blood flow velocity in the internal carotid or middle cerebral artery greater than 200 cm per second have a very high risk for stroke. TCD should be used to screen all children with SCD, and children with high velocities should be started on chronic transfusion therapy.

Who is at risk for stroke?

Someone with only one gene which causes SCD has sickle trait and is usually free of symptoms because the normal hemoglobin (Hb A) counteracts the sickle hemoglobin (Hb S). If both genes controlling hemoglobin formation are the sickle type, the person has homozygous SCD. In rare cases, a person may have one S-type gene but no other gene at all, referred to as sickle beta thalassemia disease. These two types of SCD can be associated with stroke.

Children with SCD are 200 to 400 times as likely to suffer a stroke, compared to children without SCD or congenital heart disease.

The Cooperative Study of Sickle Cell Disease (CSSCD), a large prospective study, confirmed that stroke is a constant threat after age 2, but the incidence is highest in the middle of a child's first 10 years of life. About 11% of all children with homozygous SCD will develop stroke by 20 years of age.

Some characteristics of SCD are associated with an increased risk of stroke, and include low hemoglobin, elevated white blood cell count, frequency of acute chest syndrome, and history of transient ischemic attack

How many children with sickle cell disease have stroke in the United States?

Of the 2000 children with SCD born in the US each year, about 10% will develop stroke by adulthood. Perhaps as many as one in five will have abnormal areas on magnetic resonance imaging scans of the brain that suggest some stroke-like damage has occurred in the past.

What causes stroke in sickle cell disease?

The most prominent manifestation results from large artery disease. Stroke in children with SCD is not well understood, but one theory is

that stroke usually happens when major arteries of the brain are narrowed or blocked

Many patients with an infarction have abnormal cerebral blood vessels. In general, the vessels that feed the brain (carotids and vertebrobasilar) are normal in their cervical portions. Stenosis or occlusion, however, often affects the distal internal carotid (dICA) and middle cerebral arteries (MCA). In most cases the vertebrobasilar system, even if the cerebral cranial portion, remains relatively normal.

Injury to the endothelium over time, possibly relating to red blood cell adherence to the endothelium and circulating inflammatory factors and white cells, may cause narrowing of vessels. The narrowing can be shown on angiography, and when it is significant, can be detected by TCD.

At least 20% of patients with no history of stroke, no symptoms, or readily evident signs of brain injury, will have an abnormal MRI usually showing small lesions in the white matter which are associated with decreased performance in neuropsychological testing. These silent strokes may also indicate an increased risk of clinically evident stroke damage.

In other cases, the arterial disease may cause clots which go further upstream and block arteries, causing stroke. Small arteries in the brain may also be blocked by sickled red blood cells. Rarely, stroke may be caused by the rupture of a blood vessel, causing a brain hemorrhage.

In SCD, children are most likely to have infarctions, but may have hemorrhages, often with fatal consequences. Multiple strokes cause cumulative damage and can result in severe physical and mental impairment.

Children with SCD who present with acute stroke symptoms require urgent evaluation and are usually treated with hydration and exchange transfusion.

INFECTION leads to a hypercoagulable state and has been found to be a risk factor for cerebrovascular disease. CNS infection and systemic infection are perinatal risk factors.

Meningitis and encephalitis were among the most common risk factors in children hospitalized with stroke in California between 1991 and 2000.

Brain abscess, sepsis, HIV, infection with Mycoplasma pneumoniae, and parvovirus B19 infections have been associated with stroke in children.

VASCULAR DISORDERS - 23% of children with arterial ischemic stroke in one study

Central nervous system vasculitis:

can lead to arterial thrombosis, cerebral venous thrombosis, or intracranial hemorrhage. Inflammation of the cerebral vessels produces stenosis or occlusion and is caused by a variety of conditions such as infections, autoimmune diseases, drug abuse, radiation, or idiopathic disorders.

The most common cause of CNS vasculitis is bacterial meningitis. Cerebral infarction is found in 12 to 27% of children with bacterial meningitis. These children are more prone to seizures, and their outcomes are poor. Risk factors include high CSF white cell count, hypoglycorrhachia, age below 12 months, and delayed treatment. Antibiotic treatment should be started as early as possible. Steroids before the first dose of antibioties may reduce the risk of neurologic and audiologic impairment. CNS vasculitis is seen in most children with tuberculous meningitis, and cerebral infarction in the basal ganglia area is common. Septic embolism caused by bacterial endocarditis can cause CNS vasculitis and stroke.

Several cases of childhood stroke following chickenpox infection have recently been reported. These cases share similar features. They all occur in children younger than 10 years, the infarcts occur in the basal ganglia or internal capsule, and most occur within 9 months of the rash. Focal stenosis, occlusion, or segmental narrowing is seen in the proximal anterior and middle cerebral arteries. Two recent studies have confirmed this association. A retrospective study from London revealed that 17% of children with stroke had history of chickenpox within 6 months of the ictus. A French case-control study showed a significant statistical link between recent varicella and idiopathic arterial stroke. Two-thirds of children in the stroke group had varicella within 9 months prior to the stroke compared to 9% in the control group. CSF cell count, protein, and glucose are often normal, but intrathecal varicella-zoster antibodies have been identified in three children. Possible mechanisms of stroke after chickenpox are vasculitis, transient hypercoagulable state, or sympathetic stimulation. Stroke recurrence is rare, but transient ischemic

attacks have been reported. Optimal treatment remains unclear. Steroids and heparin and antiplatelet agents have been used. Adults with herpes zoster ophthalmicus can suffer delayed ipsilateral cerebral infarction caused by cerebral angiitis.

The incidence of symptomatic cerebrovascular disease in children with AIDS is 1.3% per year, but autopsy studies have shown a higher rate of some type of cerebrovascular lesion including arteriopathy.

AUTOIMMUNE DISORDERS can cause focal deficits as a result of cerebral venous thrombosis, arterial thrombosis, or intracerebral hemorrhage. Cerebrovascular disease is seen in about 6% of adults with lupus, but a pediatric study identified only 2 of 120 children with lupus with cerebrovascular occlusion. Some cases are caused by vasculitis, but other pathologic processes need to be considered. Antiphospholipid antibodies, infections, complications of treatment, Libman-Sacks endocarditis, and thrombotic thrombocytopenic pupura can all cause stroke in patients with lupus. Neurovascular and thromboembolic complications, including vasculitis, were seen in 3% of children with inflammatory bowel disease.

Takayasu arteritis is an inflammatory disease of unknown etiology involving the aorta and its branches. Young Asian females are most often affected, and stroke is seen in 5 to 10% of these patients. The mechanism of cerebral infarction in this disorder is embolic or thrombotic. Immunosuppressive therapy with steroids and azathioprine improves outcome. Cerebral infarction has also been reported in Kawasaki disease and polyarteritis nodosa. Few

pediatric cases of isolated angiitis of CNS have been reported. Without immunosuppressive therapy this disease is fatal.

Recent illicit drug use is found in 12% of young adults with ischemic stroke. Cerebral vasculitis has been associated with cocaine abuse and overdose of diet pills.

Lastly, cerebral radiation necrosis is a delayed CNS injury caused by small-vessel vasculitis. This is a progressive disorder that leads to death or disability. Treatment modalities include anticoagulation and hyperbaric oxygen.

ARTERIOVENOUS MALFORMATIONS

Moyamoya Disease

Moyamoya disease (MD) is a chronic progressive occlusive cerebrovascular disease of unknown etiology with typical angiographic features including stenosis or occlusion of the bilateral distal internal carotid arteries or the adjacent anterior, middle, or posterior cerebral arteries. There is a secondary formation of abnormal collateral vascular network (moyamoya vessels) at the base of the brain. The stenosis is caused by fibrous intimal thickening and fragmentation of the internal elastic lamina. Angiographic and histologic studies demonstrate similar changes in extracranial vessels. Several systemic disorders such as sickle-cell disease, neurofibromatosis, trisomy 21, tuberculosis, pharyngitis, fibromuscular dysplasia, aortic coaretation, cranial trauma, and irradiation have been associated with moyamoya vessels. This is often classified as angiographic moyamoya or moyamoya syndrome, and the patients have similar clinical features to those of MD.

MD was once believed to be specific to the Japanese. Lately increasing number of cases have been reported in other parts of the world. Epidemiologic studies from Japan show annual incidence of 0.35 per 100,000, with female to male ratio of 1:8 and peak age 10 to 14 years. Family history was found in 10% of patients. MD is rare in other races but has been reported in all ethnic groups showing similar epidemiologic, clinical, and radiologic features to those of Japan.

Children present with recurrent and progressive cerebral ischemia, whereas adults are more likely to develop cerebral hemorrhage. Intellectual decline, seizures, movement disorders, and headaches are also noted.

Diagnosis of childhood MD can usually be made by MR imaging and MRA. Conventional cerebral angiography is performed if there is need for surgical intervention. EEG shows the re-build-up phenomenon, a delayed return to baseline pattern, in many children with MD. Transcranial Doppler patterns correlate well with the clinical progression of the disease and can be helpful in the management of patients with MD. Positron emission tomography (PET) and proton magnetic resonance spectroscopy (MRS) are useful methods to evaluate cerebral hemodynamics and metabolism in children with MD.

No curative treatment is known for MD. In the acute phase patients with ischemic or hemorrhagic stroke should receive symptomatic treatment. Hyperventilation caused by heavy crying should be avoided because the vasoconstriction can worsen symptoms. Treatment modalities include medical treatment with vasodilators or anticoagulants, surgery, or observation. There are no randomized trials comparing surgery and medical treatment.

Revascularization surgery is often used for repeated ischemic episodes. The most common and successful procedure is encephalo-duro-arterio-synangiosis (EDAS). A branch of the superficial temporal artery is sutured into the dura over the affected hemisphere to promote formation of anastomoses with cortical arterial branches. EDAS and its modified versions decrease the frequency of ischemic attacks and prevent deterioration in mental capacity. The optimal treatment plan for hemorrhagic MD is controversial, but often emergency ventricular drainage and evacuation of hematoma are necessary.

Transient ischemic attacks occur frequently during the first 4 years and decrease thereafter. Neurologic deficits and intellectual deterioration increase with time. Permanent deficits or poor outcome is found in 45% of children with MD, and poor prognosis correlates with early age at onset and hypertension. Early indirect revascularization surgery in children with ischemic MD may prevent neurologic deficits and improves function.

ARTERIAL DISSECTION,

Cervicocephalic arterial dissections are among the major causes of stroke in childhood and adolescence. Arterial dissections occur when blood penetrates into the arterial wall through an intimal tear. The intramural hematoma splits the media, extends along the artery, and leads to stenosis or occlusion. Dissections can be traumatic or spontaneous and often involve more than one vessel. Because the trauma is often trivial, underlying arteriopathy is often suspected but rarely demonstrated. Dissections affect the internal carotid arteries (ICA) more frequently than vertebral arteries (VA) and the extracranial

arteries more often than the intracranial vessels. However, intracranial arterial dissections are relatively more common in children compared to adults.

Cervicocephalic arterial dissection was found in 20% of French children with arterial ischemic stroke and in 6% of cases in a British childhood and adolescent stroke population. Dissections leading to ischemic stroke are more common in young adults than children.

Neurologic manifestations are related to luminal narrowing by the dissection or from artery-to-artery embolism from the dissection site. Young patients with cervicocephalic arterial dissection present with focal cerebral ischemic symptoms often preceded by ipsilateral headache, neck, or eye pain. Ophthalmologic manifestation such as Horner syndrome and transient monocular blindness are more frequent in adults with ICA dissection.

Cervicocephalic arterial dissection should be considered in any child with stroke, especially when there is history of antecedent trauma to the neck, intraoral trauma, fibromuscular dysplasia, congenital heart disease, or in otherwise idiopathic cerebral or retinal infarction with or without hemicrania. Dissections of the ICA and VA are most accurately diagnosed by cerebral angiography. The angiographic features include the string sign, which is an elongated irregular narrowing of the arterial lumen, tapered occlusion, but rarely a double lumen. MR imaging is a sensitive test in the diagnosis of cervicocephalic arterial dissection, especially if thin T_1-weighted sections are obtained in axial and coronal planes with the fat-suppression technique. MRA can show arterial stenosis, but intimal irregularities and small aneurysms can be

missed. Duplex sonography is a noninvasive and simple test and, if combined with Doppler examination, is sensitive in the diagnosis of dissection.

There are no prospective randomized studies that have addressed the efficacy of treatments for cervicocephalic dissections. Most strokes associated with cervical artery dissection occur within 2 weeks and are presumed to be thromboembolic. Early anticoagulation prevents clinical deterioration in adults with ICA dissection and is recommended for a few months by most authors. Anticoagulation is not advised in dissections of the intracranial vessels because of risk of subarachnoid hemorrhage. The recurrence risk at 10 years for all age groups is 12%, higher for younger than older patients. According to Schievink's study on spontaneous dissections in childhood and adolescence, complete recovery or minimal deficit occurred in 90% of cervical artery dissections compared to 60% of intracranial artery dissection.

METABOLIC STROKE

INTRODUCTION

Metabolic problems are a rare cause of pediatric stroke. Homocystinuria and Fabry disease cause vascular occlusion; other metabolic disorders do not cause vascular insufficiency and are more properly termed strokelike episodes. As listed in Table 25-15, metabolic strokes can be caused by organic acidurias, mitochondrial abnormalities, lysosomal disorders, and urea cycle defects.

Homocystinuria arises from one of several enzymatic defects. In the classical autosomal-recessive form, deficient cystathionine beta-synthase prevents the catabolism of cystathionine to cysteine, causing increased urinary homocystine

and methionine. Most children with this disorder have mental retardation, ectopia lentis, marfanoid appearance, recurrent thromboembolic events, and severe atherosclerosis. The latter problem is often fatal in untreated patients. Homocystinemia injures vascular endothelium, leading to thrombus formation. Strokes are secondary to arterial or venous thrombosis or arterial embolism. Treatment is dietary with pyridoxine supplementation and methionine restriction.

Less severe elevations in serum homocystine are a cause of stroke in young adults and possibly children. These patients may be heterozygotes or may have other enzymatic defects. In addition, nutritional deficiencies in folate, vitamin B_{12}, and vitamin B_6 may cause hyperhomocystinemia. Several diseases (chronic renal failure, hypothyroidism, pernicious anemia, leukemia) and drugs (methotrexate, phenytoin, theophylline, cigarette smoking) increase plasma homocystine concentration. Cardo and colleagues reported elevated plasma total homocystine levels in 36% of children with acute ischemic stroke. A case-control study in Dutch children reported increases in 18% of the children with ischemic stroke. Homocystine levels were also increased in patients with sickle-cell disease and stroke. Total serum homocystine should be measured in every child with acute ischemic stroke. Some experts also suggest doing a methionine loading test in children with ischemic stroke of undetermined etiology and normal total homocystine.

Any mitochondrial encephalopathy can present with a strokelike episode or can have these as part of the clinical syndrome. MELAS usually presents with episodic headache and emesis lasting hours to days. Transient hemiparesis or

hemianopsia often follows. It usually presents in children between 5 and 15 years but can have onset in infancy. Most children have proximal muscle weakness and progressive neurologic deterioration. Strokes usually occur in the posterior cerebrum with relative sparing of white matter; they do not have a vascular distribution. Some children have calcifications in the basal ganglia. Increased CSF lactate supports the diagnosis, but muscle biopsy and molecular blood analysis are required for confirmation. Most patients have a defect in complex I, but multiple defects of respiratory chain enzymes have been reported. The most common mutation is in tRNA at mtDNA position 3243.

Fabry disease is a rare, sex-linked lysosomal disorder. A deficiency of α-galactosidase causes accumulation of ceramidetrihexoside in vascular endothelium, leading to progressive arterial narrowing, ischemia, and infarction. Stroke usually occurs in adults but has been reported in hemizygous adolescents. Ischemia occurs first in hemispheric white matter or deep gray matter, areas supplied by long, thin end arteries. Other features of the disease include pain in the extremities, abdomen, and joints; renal failure; and hypertension. Renal transplantation improves biochemical function, but its effect on cerebrovascular disease is unknown.

ORNITHINE TRANSCARBAMYLASE (OTC) DEFICIENCY is a urea cycle defect that presents in infancy with hyperammonemia and rapidly progressive neurologic dysfunction. Females with partial OTC deficiency can present in adolescence with migraine, ischemic stroke, or hyperammonemia. Treatment is with a protein-restricted diet.

MOLYBDENUM COFACTOR DEFICIENCY is an even rarer disorder with combined deficiencies of sulfite oxidase, xanthine dehydrogenase, and aldehyde oxidase. Affected infants have acquired microcephaly, seizures, and hypotonia. Most die during infancy; survivors have severe mental retardation, choreoathetosis, and spasticity. Imaging studies reveal cystic lesions in the white matter and cortex. Isolated sulfite oxidase deficiency has similar clinical and radiographic features.

CAUSES OF HEMORRHAGIC STROKE IN A CHILD

Hemorrhagic Stroke

Hemorrhagic stroke in children is as common as ischemic stroke. Bleeding occurs after rupture of normal blood vessels in children with head trauma or coagulopathies and abnormal vessels in patients with vascular malformations or aneurysms. Bleeding is classified as either subarachnoid, ie, into the subarachnoid space around the brain, or intraparenchymal, ie, into the brain parenchyma. Many patients have both subarachnoid and intraparenchymal hemorrhage. The disorders causing hemorrhagic stroke are listed in Table 25-16. The etiology of a hemorrhagic infarction can usually be identified. Treatment is often surgical.

- Intraparenchymal hemorrhage usually presents with headache, focal neurologic signs, seizures, and altered consciousness. Small hemorrhages may have very subtle clinical signs, but large bleeds usually cause coma. In neonates, seizures and signs of increased intracranial pressure are more common. Subarachnoid hemorrhage usually presents with the sudden onset

(thunderclap) of the worst headache of the child's life, followed by signs of meningeal irritation and increased intracranial pressure.

Acute hemorrhage is easily identified with CT, but within a few days the blood becomes isodense with brain parenchyma. Retinal hemorrhages may be detected on funduscopic examination. Blood is occasionally present in the spinal fluid when it is not detected with CT.

- Head trauma is the most common cause of pediatric intracranial hemorrhage. Cerebral contusion can occur alone or in association with subdural or epidural hemorrhage. Intracranial bleeding is very common in the shaken baby syndrome. Traumatic aneurysms can result from closed or penetrating head injuries. On very rare occasions, carotid-cavernous fistulas develop after fracture of the skull base. Traumatic delivery is often associated with neonatal intracranial hemorrhage.

- Coagulopathies are the next most common cause of hemorrhage. In most cases, the underlying coagulopathy is known. Very rarely, intracranial hemorrhage is the initial presentation. The hemorrhage is usually secondary to trauma, but the trauma may be very slight.

- Vascular malformations are divided into arteriovenous malformations, cavernous malformations, venous angiomas and capillary telangiectasias. The latter are a rare cause of bleeding in neurocutaneous syndromes. Arteriovenous malformations (AVMs) are comprised of abnormal primitive arteries and veins with varying amounts of intervening gliotic tissue. The malformations do not have a capillary bed between the arteries and veins. Small AVMs typically

present with focal seizures; large AVMs with seizures, headache, focal neurologic signs, and intracranial bruit. Intermittent, relatively mild headache may be caused by periodic bleeding or mass effect. Acute severe headache may be secondary to intraparenchymal hemorrhage in small or large AVMs. Ischemic infarction can result from spontaneous thrombosis or vascular steal. Vein of Galen malformations usually present in infancy with high-output congestive heart failure and failure to thrive or in early childhood with hydrocephalus. AVMs can be detected with contrast-enhanced CT, MR imaging, MR or conventional angiography. There is a 4% risk of hemorrhage from unruptured AVMs and a high risk for recurrent hemorrhage. About 10% of first hemorrhages are fatal. Embolization or surgical removal is usually required to treat AVMs. Occasionally the presenting hemorrhage successfully obliterates an AVM.

- Cavernous malformations are collections of thin-walled vessels with a single layer of endothelium, no smooth muscle or elastic tissue, and no intervening brain parenchyma. They can occur alone or in association with other vascular malformations. They present in children with seizures, focal neurologic signs, or hemorrhage. In contrast to AVMs, hemorrhage in cavernomas is rarely life threatening. Recurrent bleeding is common, especially when the cavernous malformation is in the brainstem. Cavernomas can be familial or nonfamilial. Multiple cavernomas are common in the autosomal-dominant form, and they are more likely to bleed. Cavernous malformations are rarely visualized on angiography because of the small size of the vessels and their low flow. However, on T_2-weighted MR imaging, they have a bright center with dark surrounding ring.

- Venous angiomas are composed entirely of venous structures. They are the most common vascular malformation. Most patients are asymptomatic, but they can present with seizures. Venous angiomas are easily identified with contrast-enhanced CT or MR imaging. Even when they cause seizures, they rarely require surgery. In fact, surgery can increase venous congestion and make neurologic symptoms worse.

- Saccular aneurysms are rarely symptomatic and less frequent than AVMs. They arise from an area of congenital weakness in the arteries. They can be associated with coaretation of the aorta, polycystic kidneys, Ehlers-Danlos syndrome, and Marfan syndrome. Aneurysms in children usually arise from the internal carotid artery or anterior cerebral artery. Giant aneurysms greater than 10 cm in diameter can occur. Sometimes, headache, focal neurologic signs, or hydrocephalus are the first signs; but aneurysms usually present with acute subarachnoid hemorrhage, frequently with intraparenchymal or intraventricular extension. Subarachnoid hemorrhage can cause significant vasospasm and cerebral ischemia. Surgery is the treatment of choice. Prior to surgery, patients are treated with nimodipine (to prevent vasospasm), sedation, and anticonvulsants.

THE EVALUATION OF STROKE IN CHILDREN

summary of information provided at the CHASA medical conference, 2002 by John K. Lynch, DO, NINDS. There are no published consensus guidelines on the evaluation of stroke in children, but several systematic approaches have been recommended. The evaluation should include:

- ~~Questions about any history of head trauma, neck trauma, recent infection, illness, unexplained fever or malaise, drug ingestion, developmental delay, family history of bleeding problems, and associated headache~~

- ~~Careful family history, with special attention to premature vascular disease, hematologic disease, mental retardation~~

- ~~Physical exam including head circumference in children, skin abnormalities, cardiac evaluation and carotid artery exam~~

~~MRI and MRA (CT if MR unavailable)~~

~~**If the MRI and MRA reveal an infarct, with vascular distribution**, then consider the following diagnostic tests:~~

6. ~~Echocardiogram, EKG~~

7. ~~Blood studies including CBC, Protein S, Protein C, Antithrombin III, homocysteine, lipid profile, antiphospholipid antibody, infection screen~~

8. ~~Tuberculosis screening~~

9. ~~Lumbar puncture~~

~~Transcranial Doppler~~

~~**If the MRI and MRA reveal an infarct , with non-vascular distribution, then** then consider the following diagnostic tests:~~

Plasma Lactate and pyruvate

If the MRI and MRA reveal a hemorrhage, then then consider the following diagnostic tests:

Coagulation studies

If the MRA is normal, then consider the following diagnostic tests:

Conventional Angiography

25.8.11 General Diagnostic Evaluation

The general approach to diagnostic evaluation should be question- and hypothesis-driven:

1. Is there a cerebrovascular lesion? Several disorders can mimic a stroke. Transient neurologic deficits can be seen after a seizure, with hypoglycemia or complicated migraine.

2. Is there a cerebral infarction or hemorrhage? This is crucial because etiology and treatment are different between these two processes.

3. Is it anterior or posterior circulation stroke? The prognosis tends to be worse in posterior circulation stroke. These patients may need closer observation and precautions to minimize airway compromise.

4. What is the cause of the stroke? Congenital heart disease, sickle-cell disease, and prothrombotic disorders are common. No cause can be found in about one-third of patients.

A suggested format for diagnostic workup is provided in Fig. 25-26. Our initial evaluation includes a CBC with platelet count, electrolytes and glucose, PT/PTT, toxicology screen, chest x-ray, and ECG.

Computed cranial tomography (CT), without contrast, is usually the first imaging test used because it is easy to perform and readily available. The head CT can distinguish between hemorrhage and ischemic infarction but is often normal in the first hours of infarction sometimes up to 24 hours. A subtle effacement of sulci may be the first clue to infarction. **Magnetic resonance imaging** is more sensitive than CT for early detection of infarction, but it may be normal in the first few hours. **Diffusion-weighted imaging** is good for early detection of infarction and if positive can help date the stroke. **Magnetic resonance angiography** is a good method to detect changes in blood flow in the large intracranial and cervical vessels but less reliable with small vessels. **Magnetic resonance venography** is the investigation of choice for cerebral venous thrombosis.

Once the diagnosis of stroke is established, a comprehensive workup must be performed. Because embolism is the most frequent cause of childhood stroke, a careful cardiac examination is essential

. **Transesophageal echocardiography (TEE)** may be more accurate than transthoracic echocardiography (TTE) to detect structural abnormalities of the heart. Bubble contrast should be used to detect right-left shunt.

Lumbar puncture (LP), for cerebrospinal fluid examination, should be done if infection, inflammation, or subarachnoid hemorrhage (SAH) is suspected. This

procedure should not be performed if there is clinical or neuroradiologic evidence for increased intracranial pressure. LP in a patient with a unilateral hemispheric or cerebellar lesion may lead to transtentorial or transmagnal herniation. Small SAH may be evident in the cerebrospinal fluid but not on head CT.

Transcranial Doppler (TCD) is a noninvasive and portable method used for imaging the circle of Willis and the vertebrobasilar system. TCD is useful in predicting stroke in children with sickle cell disease_, and can detect vasospasm in SAH.

Evidence for **prothrombotic state, coagulopathy or systemic inflammation** should be carefully investigated. Approximately 30% of children with ischemic stroke have abnormalities in their prothrombotic factors. Lactate and pyruvate levels should be obtained if mitochondrial disorder is suspected. CSF lactate and pyruvate values may be necessary to make the diagnosis, even though serum levels are normal. Hemoglobin electrophoresis; VDRL, HIV, and varicalla titers; and PPD should be done when clinically indicated.

The diagnostic evaluation should not stop if one risk factor is identified, because pediatric stroke patients can have more than one cause for their cerebrovascular event. If intracranial hemorrhage is detected, a neurosurgical consultation should be obtained.

Conventional angiography should be reserved for patients with nontraumatic intracranial hemorrhage or when vasculitis is suspected, if other imaging modalities have been normal. Small aneurysms, arteriovenous malformation, or

~~cavernous malformations may not show up on MR imaging or MR angiography. The angiography may not detect vascular malformations if they are surrounded by hematoma and edema. Repeating the angiography or waiting until the hematoma has resolved may be necessary in this case.~~

~~If there is no evidence for infarction or intracranial hemorrhage, other~~ **~~conditions that mimic stroke~~** ~~such as transient postictal hemiparesis, migraine, hypoglycemia, and alternating hemiplegia must be excluded.~~

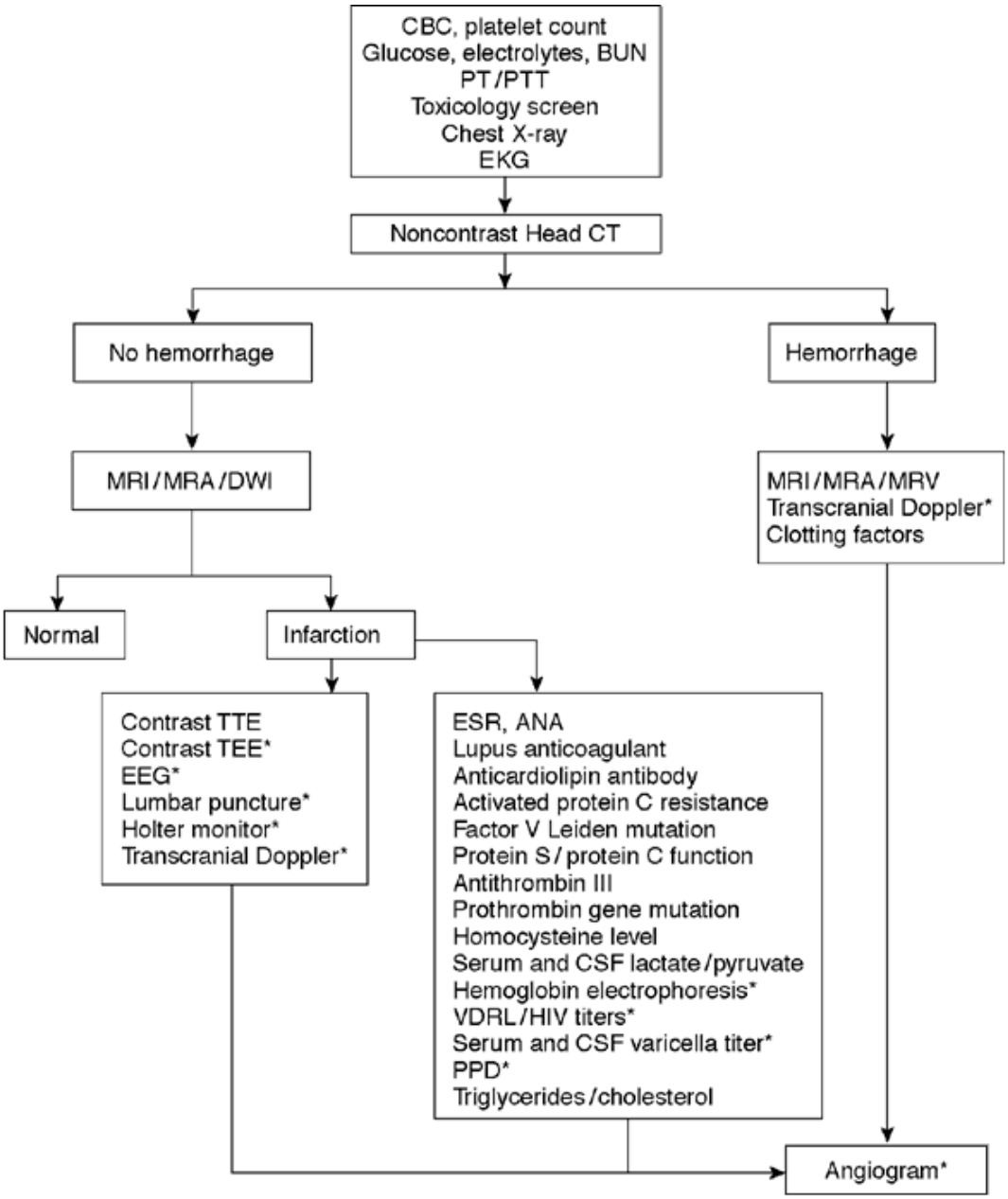


Figure 25-26. Algorithm showing the evaluation of stroke in the pediatric patient. Abbreviations—see text.

REVIEW OF LITERATURE

1.- MEAN AGE OF PRESENTATION

The mean age of presentation was 5 years in the study by **Ganesan et al 2003**, 4.3 years in the study by **Delsing et al 2001,** 8.67 years in the study by ~~a~~ **Gabis et al 2002,** 8.2 years in the study by **Jennifer et al 2007**, 5.6 ± 4.9 years in the study by **Cehung et al 2004**, 6 years ~~The~~the in the study by **Ssimma et al 2007**.

Higgins JJ et al and **Mancini J et al** stated that there was a preponderance of children less than 6 years of age at the occurrence of arterial stroke.

2.- SEX DISPARITY IN INCIDENCE OF CHILDHOOD STROKE

Ganesan et al 2003 found that 54% were males. **Kirkham et al 2004** and **Fullerton et al 2003** stated that stroke is more common in boys. In the study conducted by **Cehung et al 2004** male/female ratio was identified as 1.27:1.

,Jennifer et al 2007 stated that males (53.3%) were more likely to be affected than females (47.7%). **Ssimma et al 2007** found that ,60% were males.

Delsing et al 2001, Giroud M et al 1993, Higgins JJ et al 1991, Powell FC et al 1994 and **Mancini J et al 1997** stated that male patients slightly, but not significantly, outnumbered females.

3.- SIDE OF LESION

Lee et al 2008 stated that ,hemiplegia was more common on the right side (51%).

Delsing et al 2001 found that hemiplegia is more common on right (59%).

4.- TIME LAG TO FIRST MEDICAL CONTACT

Gabis et al 2002 stated that ,time from clinical onset to first medical contact averaged 28.5 hours, and the time to diagnose stroke averaged 35.7 hours.

5.- HEMIPLEGIA WITH APHASIA

Aphasia was an associated feature in 25% of patients in the study by **Delsing et al 2001,** ,28.6% in the study by **Obama et al 1994,** 11% in the study by **Jordan et al 2007**, 10% in the study by **Cehung et al 2004.**

6.- HEMIPLEGIA WITH SEIZURES

Seizure was an associated feature in 29% of patients in the study conducted by **Lee et al 2008,** 19% in the study by **Delsing et al 2001,** 20% in the study by **Steinlin et al,** 52% in the study by **Cehung et al 2004**, 27% in the study by **Jordan et al 2007.**

7.- HEMIPLEGIA WITH ALTERED MENTAL STATUS

Altered sensorium was reported in 16% in the study by **Delsing et al 2001**, 30% in the study by **Cehung et al 2004**, 35% in the study by **Steinlin et al** -and ,-6% in the study by -

Jordan et al 2007.

8.- HEMIPLEGIA WITH FACIAL NERVE PALSY

Obama et al 1994 found that 62.9% had facial palsy as an associated finding.

9.- AGE-RELATED VARIATION IN PRESENTING SIGNS OF CHILDHOOD ARTERIAL ISCHEMIC STROKE

Williams et al identified -

~~The conclusions derived from the study were~~ that

children had more prothrombotic causes (25% versus 14%, p = 0.03), and young adults had more dissections (3% versus 15%, p = 0.005).

Children aged 15 to 18 years had causes of ischemic stroke more similar to those in young adults.

The cause of ischemic stroke was less often identified in children than it was in young adults.

Children had more prothrombotic causes of stroke, and adults had more atherothrombotic causes and dissections.

Lacunar strokes were rare in both children and young adults.

Delsing et al 2001 found that the etiologic factors in children differ from those factors found in later life. Metabolic ~~causes~~ causes~~[2,3]~~, Moya-

Moya disease [4], hematological abnormalities [5], and infection-related strokes [6] were more common in children than in adults [7-9].

10. FAMILY HISTORY

Barreirinho et al 2003 stated that only one child had a father with myocardial infarction by the age of 45.

Cehung et al 2004 stated that only 1 patient, with moyamoya disease had a family history of stroke.

11. SUBTYPES OF ARTERIAL ISCHEMIC STROKE IN CHILDREN

Williams et al identified ~~Young adults aged > 18 to 45 years were identified from the Indiana University and Northwestern University Young Adults Stroke Registries.~~ that children had more prothrombotic causes (25% versus 14%, p = 0.03), and young adults had more dissections (3% versus 15%, p = 0.005). The cause of ischemic stroke was less often identified in children than it is in young adults. Lacunar strokes were rare in both children and young adults.

Wraig et al 2005 defined eight aetiological subtypes, as follows: (1) sickle cell disease; (2) cardioembolic; (3) moyamoya syndrome; (4) cervical arterial dissection; (5) steno-occlusive cerebral arteriopathy; (6) other determined aetiology; (7) multiple probable/possible aetiologies; and (8) undetermined etiology.

12.- ISCHEMIC STROKE

ETIOLOGY/ RISK FACTORS

Sreckovic et al 2004 stated that ~~, for the initial stroke,~~cardioembolic (33.3%) and arteriopathic processes (36.1%) were the most probable mechanisms of arterial ischemic stroke. Prothrombotic abnormalities were found in 11.1%. Underlying pathology in the remaining 19.4% was not known.

Chabrier et al 2000 described that the pathophysiologic process could be established for 78% of the children. Arteriopathic stroke (53%) was the most common cause. The arteriopathies were either progressive (moyamoya in 7%) or nonprogressive (46%). The latter form occurred in two patterns: dissection of cervicocephalic arteries (20%) and transient cerebral arteriopathy of unknown origin but probably angiitis (25%). Cardiac or transcardiac embolic stroke occurred in 12% of the series and systemic diseases in 14%.–

Lee et al 2008 stated that the risk factors included vascular disease (33%), infection (27%), metabolic disorders (18%), trauma (11%), prothrombotic states (13%), cardiac disease (10%), and mitochondrial disease (6%). Ten percent ~~(n=9)~~ had no identifiable cause. ~~Twenty-two percent~~22% of the children had more than one risk factor.

Obama et al 1994 found that the main etiological factors were: homozygous sickle cell disease (31.4%), heart disease (17.1%),

cerebral malaria (14.3%) and meningitis (14.3%). No causative factor was identified in (20%).

-**Jordan et al 2007** stated that stroke risk factors could be identified in 93% of patients. The most common risk factors were cardiac disease, infection, vasculopathy, trauma and hematological disorders. Vasculopathy included cerebral arterial abnormalities due to moyamoya disease, HIV, arterial dissection and transient cerebral arteriopathy.

Cehung et al 2004 stated that important causes included congenital heart diseases (30%), vascular diseases (26%) and hematologic diseases (28%). 12% had no determined causes.

Jennifer et al 2007 ~~, of in~~enumerated the etiologies as cardioembolic (21.5%), moyamoya (16.9%), carotid dissection (10.8%), vertebral dissection (10.8%) , prothrombotic (7.7%), post-varicella (3.1%) ~~,~~and ~~(~~1.5% ~~)~~ each of infection; pulmonary arteriovenous malformation; chemotherapy-related stroke; sickle-cell disease; vasculitis; cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL); mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke (MELAS); hypertension; and complicated migraine. The etiology was unknown in (15.4%).

R Sträter et al 1999, R Sträter et al 2002, V Ganesan et al 1996 and **U Nowak-Gottl et al 1999** stated that a single thrombophilia does not fully explain a stroke in a child, but multiple thrombophilias and thrombophilia in

patients with cerebral arteriopathy or congenital heart disease confers a higher risk of stroke.

13. -

VARICELLA INFECTION

Losurdo et al 2006 observed 4 cases of cerebrovascular disease after varicella infection.

R Askalan et al 2001, V Ganesan et al 1997, G Losurdo et al 2005 and **G Sébire et al 1999** showed that children with stroke were 18 times more likely to have had chicken pox in the previous 9 months than healthy controls were.

E Chiappini et al 2002 and **E Wirrell et al 2004** observed that ~~[66], [67], [68] and [69]~~ secondary reactivation of varicella zoster virus had been associated with stroke. ~~70~~ ~~71~~

MA Nagel et al 2007 confirmed active varicella zoster virus replication in the CNS by PCR or by antibodies in the CSF.

L.J. Kappelle et al 1989 stated that vasculitis, caused by the direct invasion of infectious agents or by the interaction of a virus with platelets, leading to thrombosis, may account for the development of infarcts.

——Seébire G et al 1999 stated that there was a significant statistical link between idiopathic arterial ischemic strokes in children and varicella-zoster virus infection.

——Hausler et al 1998 reported four previously healthy children with VZCV with ~~Clinical manifestations included s~~sudden onset of hemiparesis, motor aphasia and disturbed consciousness. ~~in previously healthy children.~~ One child had a history of chickenpox six weeks prior to the onset of stroke and a latency period of up to four years between chickenpox and the onset of stroke was found in the other three children.

——Inagaki et al reported that 9 of 16 young patients with basal ganglionic infarctions had manifested varicella 1-4 months before onset.

——H. Wanifuchi et al 1988 and L. Tucciarone et al 1992 found that in unexplained cases of childhood infarctions, episodes of inflammation, such as that due to varicella, measles, ~~s.~~, ~~, and~~ tonsillitis ~~[12,22,23],~~ or mild head trauma ~~[12]~~ in the past history have been considered to be possible antecedent factors.

14.- MINOR HEAD TRAUMA

——**Satoh et al 1991 ~~[12]~~ reported that 10 of 54 pediatric patients with cerebral infarctions had mild head trauma. Stretching of the lateral lenticulostriate perforating arteries caused by sudden rotation of the head during injury was considered to be a possible explanation for the occurrence of subcortical infarcts ~~[25]~~.**

——**Kieslich et al 2002** investigated the importance of traumatic endothelial lesions in intraparenchymal end arteries after minor head injuries. Minor head injuries can be cause and co-factor in the etiology of stroke.

15.- MULTIPLE RISK FACTORS

——**Lanthier et al 2000** stated that risk factors were variable and multiple in 24% of ischemic strokes. Ischemic stroke recurred in 8% patients with a single or no identified risk factor and in 42% of patients with multiple risk factors ($p = 0.01$). No patient with hemorrhagic stroke had multiple risk factors.

16.- SICKLE CELL ANEMIA

——**Oliveira et al 2008** concluded that cerebral infarction affected approximately 30% of all individuals with sickle cell anemia. The stroke was ischemic in all individuals and the first cerebrovascular event occurred before 6 years of age.

——**RJ Adams et al 1998** and **HJ Fullerton et al 2004** stated that in children who were at a particularly high risk of stroke, on the basis of abnormal results on transcranial doppler, chronic blood transfusion therapy resulted in a 90% reduction in relative risk of stroke.

~~[37] and [38]~~

De baun et al 2006, M Prengler et al 2002 and **JJ Strouse et al 2006** focused on the risk factors for stroke in sickle cell disease that included raised blood pressure, lower haemoglobin concentrations, high leukocyte count, previous transient ischaemic attacks, priapism, acute anaemia, recent acute chest syndrome, or transfusion within the past 2 weeks. [47] [48]

Jordan et al 2007 stated that children with sickle cell disease had a markedly increased risk of both hemorrhagic and ischemic stroke.

17. ITP

Jordan et al 2007 stated in his study that, brain hemorrhage was estimated to occur in 0.1% to 1.0% of children with idiopathic thrombocytopenia purpura. [26].

18. HEMOPHILIA

Jordan et al 2007 identified that the prevalence of intracranial (epidural, subdural, and parenchymal) hemorrhage in hemophiliac children to be between 2.9% and 12% [28], [29] and [30], with a median age at onset of 5.9 months to 2 years. [28] and [29]. Trauma was the most important risk factor for intracranial hemorrhage in children with hemophilia [28].

19. HEMORRHAGIC STROKE

Blom et al 1998 suggest that overall mortality from hemorrhagic stroke was approximately 25% in children; significant disability was present in 42% of those who survive.

..[14].20. RISK FACTORS FOR HEMORRHAGIC STROKE IN CHILDHOOD

Al-Jarallah et al 1998 and Meyer-Heim 2000 suggest that intraparenchymal hemorrhage in childhood was most often the result of arteriovenous malformation (14% to 46%), hematologic abnormality, or brain tumor. (Table 2) [15], [16] and [17]. Other etiologies include cavernous hemangioma [18], vasculopathy, vasculitis, cerebral and systemic infections, and rarely, illicit drug use..[9], [12] and [21].

Giroud et al 1993, Al-Jarallah et al 1998 and Meyer-et al 2000 reported that hematological abnormalities were the major risk factor in 10% to 30% of hemorrhagic —and include thrombocytopenia, hemophilia, and coagulopathies..

21. ISCHEMIC VS HEMORRHAGIC

10-year review of the Dijon Childhood Neurology Clinic experience (1985-1995) bGiroud et al 1997, 10-year review of the Dijon Childhood Neurology Clinic experience (1985-1995) identified studied 54 patients with arterial stroke were identified. –There were 31 cases of ischemic stroke, representing 57% of the total, and 23 cases of hemorrhagic stroke, representing 43% of the total.

Lanthier et al 2000 found that 70% of the strokes were ischemic strokes and 30% were hemorrhagic strokes.

——**Chung et al 2004** stated that 72% were ischemic and 28% were hemorrhagic stroke whereas **Simma et al 2007** stated that 73% were ischemic strokes and 27% were hemorrhagic strokes.

22.- INVESTIGATIONS

——**Husson et al 2002** concluded that contrast angiography (CA) was the reference examination for the diagnosis of cerebral arterial abnormality, but this procedure is invasive. All lesions shown by CA were present on MRA. Patients with no lesion on MRA had normal CA. Associated distal vascular lesions and degree of arterial stenosis were more accurately detected with CA. MRA is sensitive enough to provide an adequate initial evaluation of arterial brain disease in childhood.

——**Jordan et al 2007** found that a combination of magnetic resonance imaging, magnetic resonance angiography, and magnetic resonance venography images accurately identified the cause of intraparenchymal hemorrhage in 66%~~ [40]~~. Interestingly, in the same study, conventional cerebral angiography alone had a diagnostic yield of 61%.~~.~~

——**Ganesan et al 1999** suggest that conventional cerebral angiography has a continuing role in the identification of potentially treatable cerebrovascular abnormalities in children with ischemic stroke which include moyamoya syndrome~~ [1,2]~~, arterial dissection~~ [3],~~ and cerebral vasculitis~~.~~ and remains mandatory for preoperative evaluation. MRA is a sensitive imaging modality for moyamoya syndrome, for the detection of large vessel stenosis and occlusion, for screening patients

at risk [5-7], for serial monitoring in patients who are known to be affected or after surgery [8], for arterial dissection especially in combination with duplex ultrasound of the carotid vessels in the neck [3,9] and for children with sickle cell disease for whom MRA and transcranial Doppler ultrasound individually have demonstrated a high sensitivity and specificity compared with conventional angiography However, the resolution of MRA only permits examination of vessels with a diameter of 1mm [13], and detection of abnormalities in the posterior circulation is relatively poor [11].

23. THROMBOLYTIC THERAPY IN ISCHEMIC STROKE

Kirton et al (2008) by Kirton et al (2008) reported that only 1.6% of children with arterial ischemic stroke were given thrombolytics in the United States [2]. Consistent with this are studies demonstrating long delays in the diagnosis of childhood stroke, and report that the majority of children are ineligible to receive thrombolytic therapy according to adult thrombolysis criteria [3]. The benefits of intravenous thrombolysis are lost beyond 3 hours [5] and any benefit is overcome by an increasing incidence of symptomatic intracerebral hemorrhage. Anticoagulation and antiplatelet approaches to treatment, as well as neuroprotective strategies, are supported by these guidelines and existing safety data, whereas thrombolytics are not [10].

24. PROGNOSTIC FACTORS

ISCHEMIC VS HEMORRHAGIC

——**Schoenberg et al 1978** stated that although children with cerebral infarction had better survival, they experienced more residual disability than children with cerebral hemorrhage.

——**Cehung et al 2004** stated that 13.9% with ischemic stroke and 26% with hemorrhagic stroke died. Decreased level of consciousness was significant risk factor associated with high mortality rates.

——**Lanthier et al 2000** stated that risk factors were variable and multiple in 24% of ischemic strokes. Ischemic stroke recurred in 8% of patients with a single or no identified risk factor and in 42% of patients with multiple risk factors ($p = 0.01$). No patient with hemorrhagic stroke had multiple risk factors. Hemorrhagic stroke recurred in two patients (10%).

25. -PREDICTORS OF LONG TERM MORBIDITY

——**Schoenberg et al 1978** stated that although children with cerebral infarction had better survival, they experienced more residual disability than children with cerebral hemorrhage.

——In the study by **De Veber et al 2000**, the primary outcome based on Pediatric Stroke Outcome Measure assessment (PSOM) was stated as: normal, 37%; mild deficit, 20%; moderate deficit, 26%; and severe deficit, 16%. Poor outcome in children after ischemic stroke was frequent and more likely in the presence of arterial stroke, rehabilitation therapy and associated neurologic disorders, which justifies clinical trials of treatment strategies in childhood ischemic stroke.

Cehung et al 2004 stated that long-term neurologic deficits occurred among 41% of survivors, including mental retardation, epilepsy and hemiplegia. For 82% who survived, the only significant risk factor for long-term neurologic deficits was seizures at the initial presentation. Other factors, such as gender, age, other clinical features, stroke type, vascular territory, other causes, and recurrence of stroke, were all insignificant for both death and long-term deficits.

Lanthier et al . [9] reported that the coexistence of multiple stroke risk factors in children predicted poor outcome.

26. PREDICTORS OF MORTALITY

Cehung et al 2004 stated that 13.9% with ischemic stroke and 26% with hemorrhagic stroke died. Decreased levels of consciousness, hematological causes and hemorrhagic transformation (applicable only in ischemic stroke) were significant risk factors associated with high mortality rates.

Delsing et al 2001 stated that death occurred more frequently in patients with recurrent stroke (40%) than in those with nonrecurrent stroke (16%).

Dusser et al. [16] stated that children with idiopathic strokes had a better prognosis, with minor residual deficits, in contrast with severe neurologic residual impairment in children after stroke in association with cardiac disease. Alteration of consciousness with or

without seizures was reported to be a significant risk factor of immediate death after arterial stroke. ~~[17,18].~~

27.- PREDICTORS OF RECURRENCE

——**Lee et al 2008** stated that 16% had recurrent stroke, 60% of whom had underlying vascular disease. The vascular disease included moyamoya disease, CNS lupus and ill-defined vasculopathy.

——**Delsing et al 2001** stated that 22% had one or two recurrences.

——**Lanthier et al 2000** stated that risk factors were variable and multiple in 24% of ischemic strokes. Ischemic stroke recurred in 8% of patients with a single or no identified risk factor and in 42% of patients with multiple risk factors ($p = 0.01$). No patient with hemorrhagic stroke had multiple risk factors. Hemorrhagic stroke recurred in two patients 10%.

——**Sreckovic et al 2004** stated that recurrent ischemic infarction was diagnosed in 13.9%. The risk of recurrence appeared to be fivefold higher in children with cardiac disease irrespective of the coexistence of other risk factors.

——**Chabrier et al 2000** found that there was a favorable outcome in 70% of patients having stroke due to nonprogressive arterial disease and stroke due to unidentified mechanisms. In contrast, only 26% of patients with embolic

stroke, systemic disease or moyamoya had a favorable outcome. Recurrences were more frequent and severe in this latter group.

Ganesan et al 2006 concluded that clinical and radiological recurrences were common after childhood AIS. The risk of clinical recurrence was high in children with moyamoya and in those with genetic thrombophilia. Preexisting pathology, including immunodeficiency and persistent leukocytosis was a risk factor for radiological recurrence.

Fullerton et al 2007 studied the risk of recurrence in hemorrhagic stroke (HS). Overall, 10% children with HS experienced a recurrence within 5 years, despite available therapies. Whereas idiopathic HS rarely recurred, HS due to medical etiologies tended to recur acutely and children with structural lesions had a high and prolonged risk for recurrence.

Lynch et al 2004 reviewed that up to one third will have a recurrent stroke.

28. ~~.~~ COGNITIVE OUTCOME

De Schrijver et al~~.~~ ~~[15]~~ concluded that global cognitive functioning in children after arterial stroke was shifted toward lower levels.

Delsing et al 2001 stated that ~~,~~attention is impaired after childhood stroke and poorer performance was associated with an earlier age of stroke.~~109~~ Intellectual impairment was common in children with stroke that was associated with sickle cell disease. ~~108~~The laterality of stroke does not influence

neuropsychological outcome, and there was no clear relation between the location of stroke and cognitive outcome.[107]

29. OUTCOME, LONG TERM FOLLOW UP AND QUALITY OF LIFE

Chabrier et al 2000 found that there was a favorable outcome in 70% of patients having stroke due to nonprogressive arterial disease and stroke due to unidentified mechanisms. In contrast, only 26% of patients with embolic stroke, systemic disease or moyamoya had a favorable outcome. Recurrences were more frequent and severe in this latter group. More than a half of children with AIS will have neurological sequelae.[105]

Obama et al 1994 stated that ~~**,were studied from August 1984 to July 1990,**~~ the mortality rate as low (2.9%) and all the children had neurological deficit after a mean hospital stay of 15 days.

Lanthier et al 2000 stated the outcome as follows: asymptomatic, 36%, symptomatic epilepsy or persistent neurologic deficit, 45% and death, 20%.

Simma et al 2007 stated that 55% had a good overall outcome, with no neurological symptoms, normal intelligence test scores and normal quality of life ~~(Table 3)~~. In the remaining nine children (45%) with poor overall outcome, all had severe or moderate clinical neurological deficits. ~~(~~Table 4~~).~~

30.- FUTURE STUDIES NEEDED

Jordan et al 2001 stated that while research in arterial ischemic stroke and cerebral venous sinus thrombosis is expanding, hemorrhagic stroke in children remains largely unstudied. There is a paucity of literature to guide physicians who care for children with hemorrhagic stroke. Additional work is required in hemorrhagic, as well as arterial ischemic stroke in childhood. Randomized controlled trials of intervention will be essential. In hemorrhagic stroke, particularly important data that are required to plan randomized controlled trials include recent population-based data on incidence and etiology of childhood hemorrhagic stroke; information on time to presentation that may affect therapeutic options; detailed information on neurologic outcome and predictors of outcome; and Phase I and II treatment trials that include children.

JUSTIFICATION OF THE STUDY

Stroke in children differs from stroke in adults by the rarity, subtle presentation and wide differential diagnosis (Coagulation, vascular & neurological systems.

Risk factors are multiple, age-related and poorly understood and there is no established treatment protocol.

Impact of pediatric stroke is great with mortality up to 10%, risk of recurrence of arterial stroke upto 20 to 30%, risk of death, disability, reduced quality of life upto 50% (Seizures 15%, headache disorders 30%, neurologic deficits 60%).

Identification of the cause of pediatric stroke is increasing due to the availability of more sensitive imaging and the incidence is increasing due to effective management of predisposing conditions (CHD, prematurity, tumors).

AIM OF THE STUDY

Aim of the present study is to identify etiology of stroke in children in our part of world, to assess the mortality and morbidity and to follow them up for 1 to 2 years to recognize complications.

MATERIALS AND METHODS

STUDY DESIGN

Prospective cohort study

STUDY PERIOD

October 2006 - September 2008

STUDY PLACE

Department of Neurology, Institute of Child Health, Chennai

SAMPLE SIZE

68

INCLUSION CRITERIA

Acute motor weakness involving one half of the body in children between 2 months to 12 years, presenting within 3 weeks from the onset.

EXCLUSION CRITERIA

1. Old cases with history more than 3 weeks from the onset
2. Those with weakness lasting less than 24 hours

METHODOLOGY

The present study was conducted in the Institute of Cchild Hhealth and Hhospital for children, Chennai. 68 children ~~who~~ rangeding in age from 2 months to 12 years~~, who~~ presenteding with weakness ~~involving oof~~ one half of the body, ~~(hemiplegia) with onset~~ within 3 weeks of onset, were included in the study. The children were admitted

in medical wards. Initial resuscitation was done by stabilizing the airway, breathing and circulation, control of seizures with anti epileptics and appropriate anti edema measures for raised intracranial tension. Since all the children included in the present study presented beyond 3 hours from the onset of weakness, none were subjected to thrombolytic therapy.

A detailed history of the presenting illness was obtained including the onset, distribution, progression of weakness, seizures, fever, headache, vomiting, altered level of consciousness, aphasia, cranial nerve palsies, extrapyramidal movements and sensory involvement.

History of head trauma, neck trauma, recent infection, illness, unexplained fever or malaise and drug ingestion, if any, was also obtained. Significant past history, antenatal, ~~and~~ developmental history ~~were obtained.~~ and i~~I~~nformation regarding demographic data were ~~as~~ collected. Careful family history, with special attention to premature vascular disease, hematologic disease and~~,~~ mental retardation was elicited~~obtained~~.

Physical examination including head circumference ~~in children~~, neurocutaneous markers, cardiac evaluation~~,~~ and palpation of carotid arteries~~y~~ and a detailed neurological examination was done.

Severity of motor weakness was graded as below.

1. Mild – near normal power, abnormal gait and arm drift.

2. Moderate – significant weakness interfering with activities of daily living.

3. Profound – dependant for ambulation or bed ridden.

~~History of head trauma, neck trauma, recent infection, illness, unexplained fever or malaise and drug ingestion, if any, was obtained. Significant past history, antenatal and developmental history were obtained. Information regarding demographic data was collected. Careful family history, with special attention to premature vascular disease, hematologic disease, mental retardation was obtained. Physical examination including head circumference in children, neurocutaneous markers, cardiac evaluation and carotid artery examination and a detailed neurological examination was done. All children were subjected to neuroimaging MRI and MRA. Further workup was tailored based on the findings in neuroimaging.~~

All children were subjected to neuroimaging (MRI and MRA). Further workup was tailored based on the findings in neuroimaging. If the MRI and MRA reveal an infarct, with vascular distribution, then following diagnostic tests were performed - Echocardiogram, EKG, blood studies including CBC, Protein S, Protein C, Antithrombin III, homocysteine, lipid profile, antiphospholipid antibody, infection screen, tuberculosis screening, lumbar puncture and transcranial Doppler.

If the MRI and MRA reveal an infarct, with non-vascular distribution, serum lactate and pyruvate were done.

———If the MRI and MRA reveal a hemorrhage, then studies to screen for coagulation disorders were done like bleeding time, clotting time, prothrombin time and partial thromboplastin time. If the results were abnormal, then studies like factor VIII assay, factor XI assay, to rule out specific coagulation disorder were obtained.

———Presenting symptoms and underlying etiology were analyzed and children were categorized based on the etiology.

———All surviving children were neurologically examined, at the end of the follow-up period of 1 – 2 years, to determine residual impairment. Determination of residual impairment in each child was based on the findings at neurological examination at the end of the follow-up period. ———Outcome was considered favorable when children had no residual impairment.

Outcome was considered unfavorable when children had residual impairment or have died.

———Statistical analysis was done and the relation of each variable to outcome categories was analysed separately by the chi-square test. . ~~(Chicago, IL).~~

OBSERVATION AND RESULTS

1.- SEX DISPARITY

——In the present study, 42% of the cases were males and 58 % were females, which is statistically not significant (chi-square test - p=0.145) (Picture. 1)..

2.- MEAN AGE AT ONSET

——In the present study, the mean age at the onset of hemiplegia was 4.4 years.

3.- SIDE OF LESION

——In the present study, 52% of cases had right sided hemiplegia and 48% had left sided lesion, which is statistically not significant (chi-square test - p=0.808). (Picture. 2).

4.- TIME LAG FOR FIRST MEDICAL CONTACT

——The average time lag from the onset of weakness to first medical contact in our study is 70 hrs.

5.- PAST HISTORY

——In the present study, 2 cases had a history of chicken pox 3 months before the onset of hemiplegia, one case had chicken pox 15 days before and one case had a history of measles 15 days back.

6.- FAMILY HISTORY

——In the present study, 1 case had a family history of recurrent stroke in father and the child presented with regression of milestones.

7.- HEMIPLEGIA WITH APHASIA

——In the present study, 28.5% with right sided weakness had aphasia whereas 9% with left sided weakness had aphasia.

8.- HEMIPLEGIA WITH SEIZURES

——In the present study, 41% of the cases had seizures either focal or generalized and 59% of the cases were seizure free. Among the patients who had seizures, 68% had residual motor weakness whereas only 60% of cases who were seizure free had residual weakness. Association of seizures with neurological outcome is not statistically significant (p=0.508) (Picture. 3)..

Seizures	Number	Good outcome	Poor Outcome	X2=0.437
Focal or generalized seizures	28(41%)	9(32%)	19(68%)	p=0.508 NS
No seizures	40(59%)	16(40%)	24(60%)	

NS – not significant

9.- HEMIPLEGIA WITH FACIAL PALSY

——In the present study 39.7% of patients with hemiplegia had facial palsy

10.- CONSCIOUSNESS

———In the present study, at the onset of illness, 10.3% of cases were drowsy and 7.3% of cases were unconscious. 85.3% of cases who were drowsy at the onset and 80% of cases who were unconscious at the onset had residual weakness whereas only 55% of patients who were alert at the onset had residual weakness. Association of altered level of consciousness with neurological outcome is statistically not significant (p=0.195) (P.icture. 4).

Consciousness	Number	Good outcome	Poor outcome	X2=3.270
Alert	56(82.4%)	25 (45%)	31 (55%)	p=0.195 NS
Drowsy	7(10.3%)	1 (14.2%)	6 (85.3%)	
Unconscious	5(7.3%)	1 (20%)	4 (80%)	

NS – not significant

11. -SEVERITY OF MOTOR WEAKNESS

——In the present study, 67.4% of patients with moderate weakness and 88.5% of cases with severe weakness had residual weakness whereas only 35.7% of cases with mild weakness had residual weakness. (Picture . 5).

Severity of motor weakness	Number	Good Outcome	Poor outcome	X2=6.92887
Mild	14(20.6%)	9 (64.3%)	5 (35.7%)	p=0.031 S
Moderate	46(67.6%)	15 (32.6%)	31 (67.4%)	
Severe	8(11.8%)	1 (12.5%)	7 (88.5%)	

S - significant

12.- NEUROIMAGING

——In the present study, MRI revealed infarct in 83.8%, hemorrhage in 10.328.5% and space occupying lesion in 5.9%.

MRI	Number
Infarct	59(83.8%)
Hemorrhage	5(10.3%)
SOL	4(5.9%)

13.- BLOOD COUNT

Peripheral smear	Number	Good outcome	Poor outcome
Anemia	17	9	8
Leukemia	1	0	1
Thrombocytopenia	1	0	1
Polycythemia	3	0	3

14. CAUSES OF HEMIPLEGIA

——The table below shows the observation of the etiology of hemiplegia in the present study. Underlying cardiac disorder, either congenital or acquired was observed in 16% of cases and was the most common risk factor followed by prothrombotic factors in 14.7%, which is statistically significant (chi-square test - p=0.036). Multiple risk factors were observed in 16% of cases (Picture. 7 & 8)..

Eitiology		Number	Good Outcome	Poor outcome
Cardiovascular ~~Cyanotic CHD~~ ~~Acyanotic CHD~~ ~~Valvular heart disease~~ ~~RBBB~~	Cyanotic CHD	4	0	4
	Acyanotic CHD	4	0	4
	Valvular heart disease	2	2	2
	RBBB	1	1	0
Prothrombotic ~~Protein C deficiency~~ ~~Protein S deficiency~~ ~~APLA~~ ~~Homocystinuria~~	Protein C deficiency	0	0	0
	Protein S deficiency	4	3	1
	APLA	4	1	3
	Homocystinuria	2	0	2
Vascular ~~Nonspecific Vaseulitis~~ ~~Moya moya disease~~ ~~Hypoplasia of ICA/MCA~~	Nonspecific Vasculitis	3	2	1
	Moya moya disease	2	0	2
	Hypoplasia of ICA/MCA	3	0	3
Anemia ~~Sickle cell~~ ~~Thalassemia major~~ ~~Iron deficiency anemia~~	Sickle cell	1	0	1
	Thalassemia major	2	1	1
	Iron deficiency anemia	1	1	0
Minor head injury		4	3	1
Multiple risk factors		11	4	7
Bleeding ~~ITP~~ ~~VWD~~ ~~Late HDN~~	ITP	1	0	1
	VWD	1	0	1
	Late HDN	1	0	1
Space occupying lesion ~~Tuberculoma~~ ~~Pilocytic astrocytoma~~	Tuberculoma	3	3	0
	Pilocytic astrocytoma	1	0	1
Infections ~~Bacterial meningitis~~ ~~Tuberculous meningitis~~	Bacterial meningitis	1	0	1
	Tuberculous meningitis	1	0	1
	Encephalitis	1	0	1
	Attico antral cholesteatoma	1	1	0

~~Encephalitis~~ ~~Attico antral cholesteatoma~~				
Metabolic ~~Mitochondrial~~	Mitochondrial	1	1	0
Not known		8	7	1

15.- CLASSIFICATION OF CAUSES OF HEMIPLEGIA ~~STROKE~~

——In the present study, 769.4% of cases were ischemic stroke, 170.3% were hemorrhagic stroke, 5.8% were due to space occupying lesions, 5.8% were due to infective etiology and 1.7% was due to metabolic cause. (Picture. 9).

Causes	Number	Percentage
Ischemic	54	769.4%
Hemorrhagic	5	107.3%
Space occupying lesion	4	5.8%
Infective	4	5.8%
Metabolic	1	1.7%

16.- CAUSES OF ISCHEMIC STROKE

In the present study, multiple risk factors were identified in 20.3% of ischemic stroke and cause was not identified in 11.1%.

Causes of ischemic infarct	Number	Percentage
Single cause	37	68.6%
Multiple cause	11	20.3%
Cause not known	6	11.1%

16A. ISCHEMIC STROKE - MULTIPLE CAUSES

The multiple risk factors that were observed in 11 cases (20.3 %) and their outcome with regard to motor weakness are listed below.

Multiple causes	Outcome
Protein C, protein S, APLA	Good
Moya moya, homocystinuria	Poor
Beta thalassemia, sickle cell	Poor
APLA, dyslipidemia	Poor
MVP, positive family history	Poor
Endocardial cushion defect, PHT, right MCA	Poor

hypoplasia	
TGA, VSD, IE	Poor
Protein S, APLA	Good
APLA, lactate, pyruvate	Good
Protein C, protein S	Poor
Lactate, pyruvate, triglycerides	Good

——Among patients with multiple risk factors, 63.7% had poor outcome.

	Number	**Good outcome**	**Poor outcome**	x^2 p=0.366 NS
Multiple risk factors	11	4 (36.3%)	7 (63.7%)	

16B. ISCHEMIC STROKE - SINGLE CAUSE

——In the present study, 20.4% of cases had underlying cardiac disorder, either congenital or acquired followed by prothrombotic factors identified in 18.5% of cases, vascular etiology in 14.8%, miscellaneous causes in 14.8%, multiple risk factors in 20.4% and cause unknown in 11.1%.

Causes of ischemic stroke		Number	Percentage
Cardiovascular ~~Cyanotic heart disease~~ ~~Acyanotic heart disease~~ ~~Valvular heart disease~~ ~~RBBB~~	Cyanotic heart disease	~~411~~ ~~4~~	11(20.4%)
	Acyanotic heart disease	4	
	~~V~~alvular heart disease	2	
	RBBB	1	
Prothrombotic ~~Protein c~~ ~~Protein s~~ ~~APLA~~ ~~Homocystinuria~~	Protein C	0~~10~~ ~~0~~	10(18.5%)
	Protein S	4	
	APLA	4	
	Homocystinuria	2	
Vascular eitiology ~~Nonspecific vasculitis~~ ~~Moya moya syndrome~~ ~~Hypoplasia of ICA/MCA~~	Nonspecific vasculitis	~~8~~ 3	8(14.8%)
	Moya moya syndrome	2	
	~~Hypo~~plasia of ICA/MCA	3	
Anemia ~~Sickle cell anemia~~ ~~Thalassemia major~~ ~~Iron deficiency anemia~~	Sickle cell anemia	~~5~~ 1	4(7.4%)
	Thalassemia major	2	
	Iron deficiency anemia	1	
Minor head injury		4	7.4%
Multiple causes		11	20.4%

Not known		6	11.1%

17.- CAUSES OF HEMORRHAGIC STROKE

——In the present study 60% of hemorrhagic stroke were due to blood dyscrasias and in 40% of cases, cause could not be identified (Picture. 10)..

Causes of hemorrhagic stroke ~~Causes of hemorrhagic stroke~~		Number	Percentage
Blood dyscrasias	~~Blood dyscrasias~~ Idiopathic thrombocytopenic purpura	1	60%
	Von Willebrands disease	1	
	Late onset hemorrhagic disease of newborn	1	
Not known	~~Not known~~	2	40%

18.- SPACE OCCUPYING LESION

——Space occupying lesion accounted for 5.8% of cases, 75% of which were due to tuberculoma and 25% were due to pilocytic astrocytoma.

Cause	Number	Good outcome	Poor outcome
Tuberculoma	3	3	0
Pilocytic astrocytoma	1	0	1

19.-INFECTIOUS ETIOLOGY

20.

———Infection accounted for 5.8% of cases, 2 cases were due to meningitis, 1 case was due to encephalitis and 1 case was due to atticoantral cholesteatoma.

Cause	Number	Good outcome	Poor outcome
Bacterial meningitis	1	0	1
Tuberculous meningitis	1	0	1
Encephalitis	1	0	1
Attico antral cholesteatoma	1	1	0

20.- OUTCOME

——In the present study, 60.2% had residual weakness on follow up lasting for a period of 1 to 2 years. Among children with ischemic infarct 44.4% had no motor deficit and 55.6% had residual weakness. Among children with hemorrhagic infarct 20% had no residual weakness and 80% had residual weakness. Among cases with space occupying lesion all the cases with tuberculoma had no residual weakness and the one with pilocytic astrocytoma had residual weakness. Among cases with infectious etiology, the one due to cholesteatoma had no residual weakness and cases with meningoencephalitis had residual weakness.

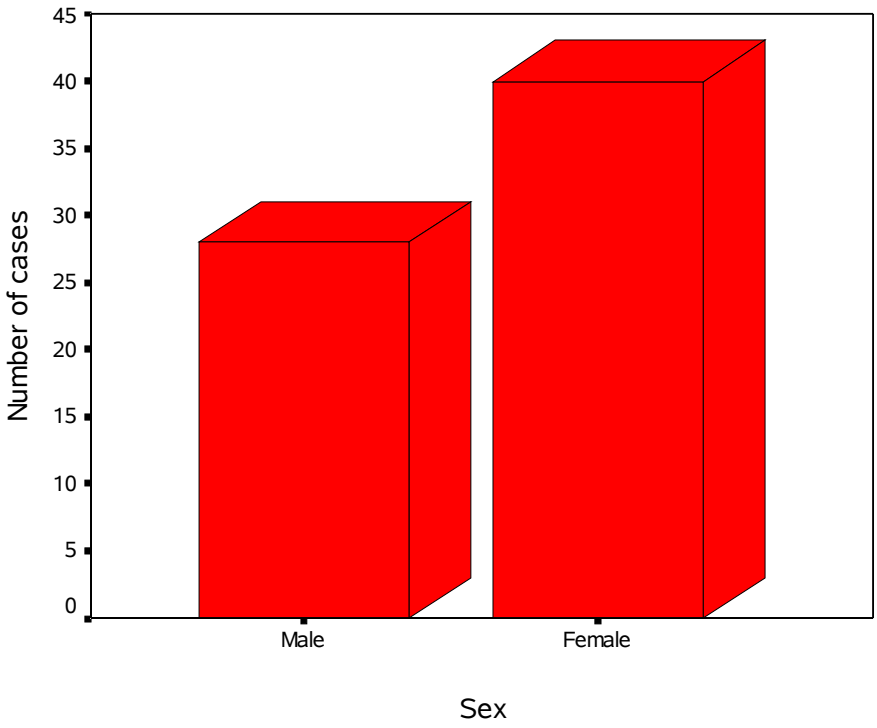
Cause	Number of cases	Good outcome	Poor outcome
Ischemic	54(79.4%)	24(44.4%)	30(55.6%)
Hemorrhagic	5(7.3%)	1(20%)	4(80%)
Space occupying lesion	4(5.8%)	3(75%)	1(25%)
Infectious	4(5.8%)	1(25%)	3(75%)
Metabolic	1(1.7%)	1(100%)	0

Mortality occurred in 2 cases (3%). One of them was a 5 year old child, a case of cyanotic congenital heart disease (transposition of great arteries) with infective endocarditis and had infarct in MCA territory. The other was a 4 year old child who died on the day of admission, in whom the cause of hemiplegia was not identified.

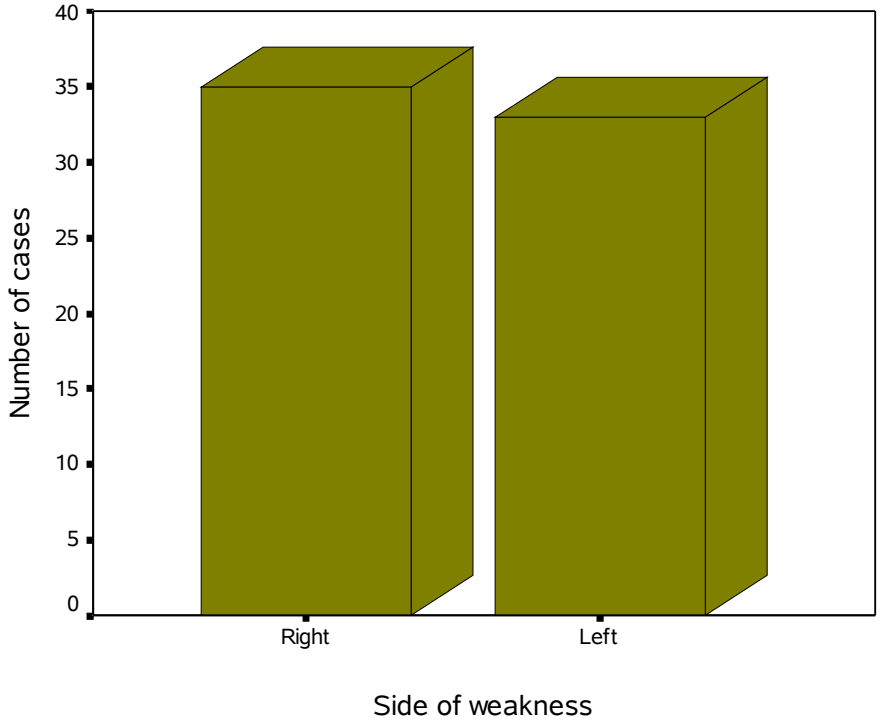
21.- RECURRENCE OF STROKE

In the present study, 1 case (3%) with homocystinuria had recurrence of stroke on follow up.

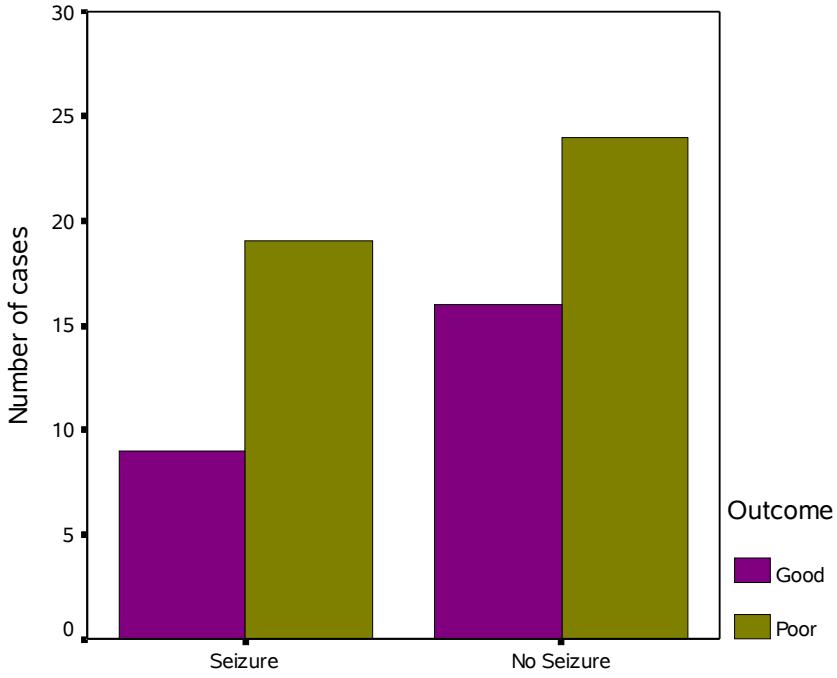
SEX DISTRIBUTION



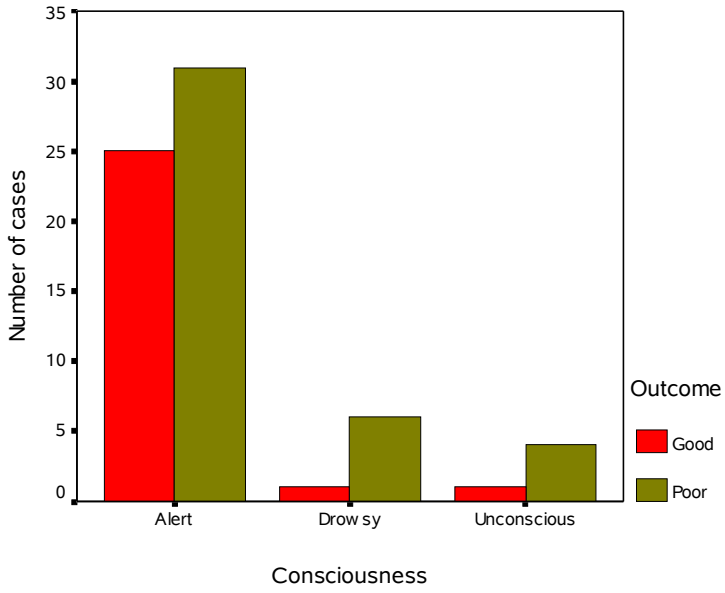
SIDE OF WEAKNESS



OUTCOME WITH RELATION TO SEIZURES AT ONSET



OUTCOME WITH RELATION TO CONSCIOUSNESS AT ONSET



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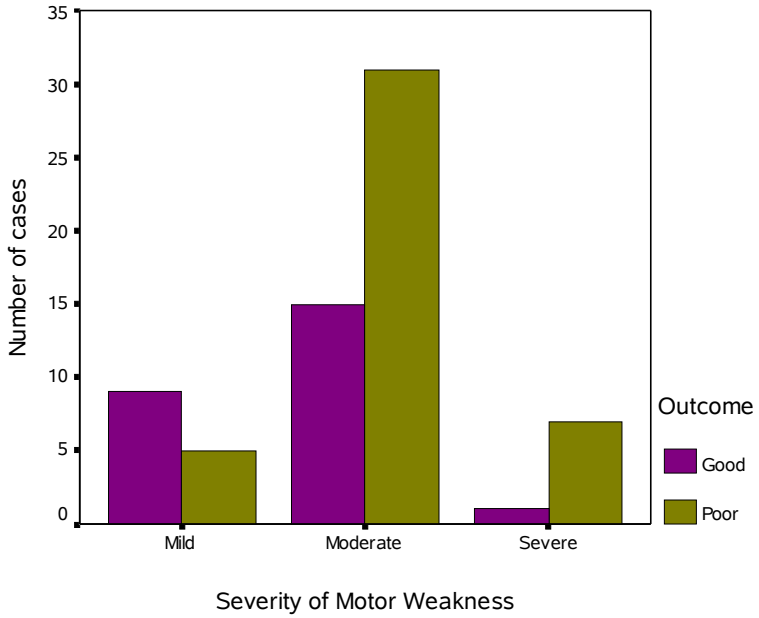
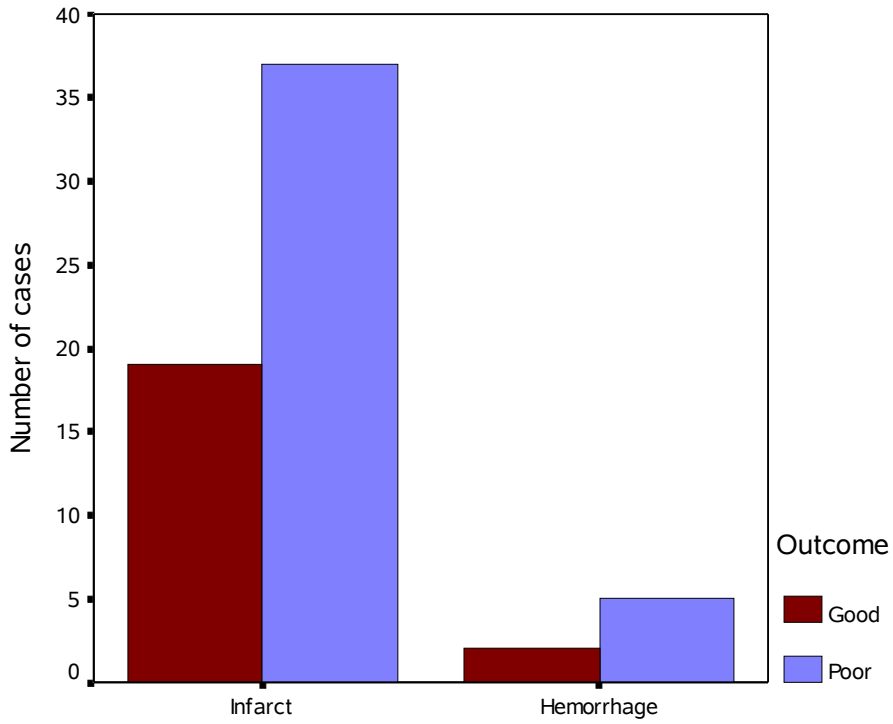
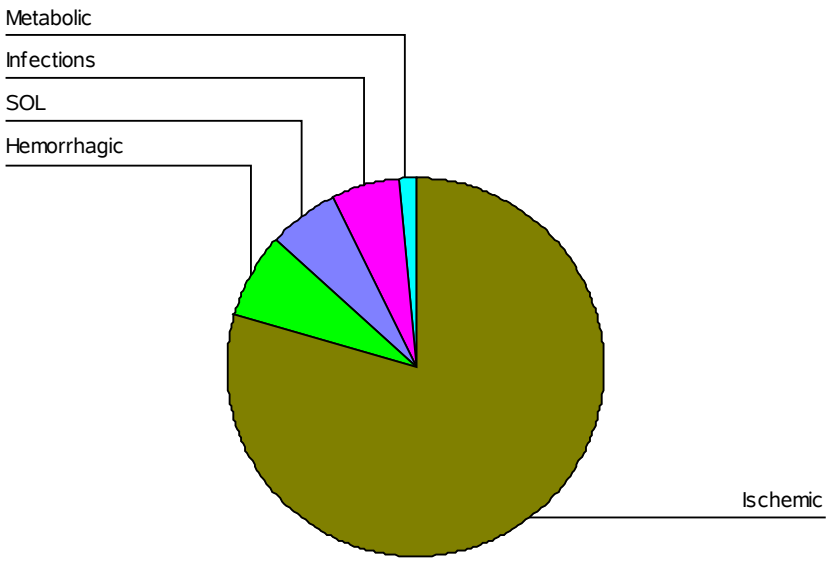


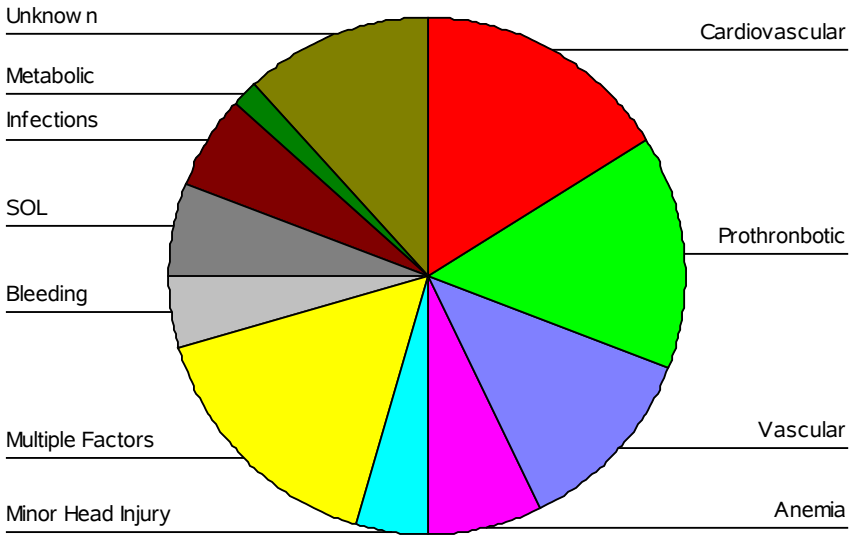
OUTCOME OF ISCHEMIC VS HEMORRHAGIC INFARCT



~~ETIOLGY OF HEMIPLEGIA~~



ETIOLOGY OF HEMIPLEGIA



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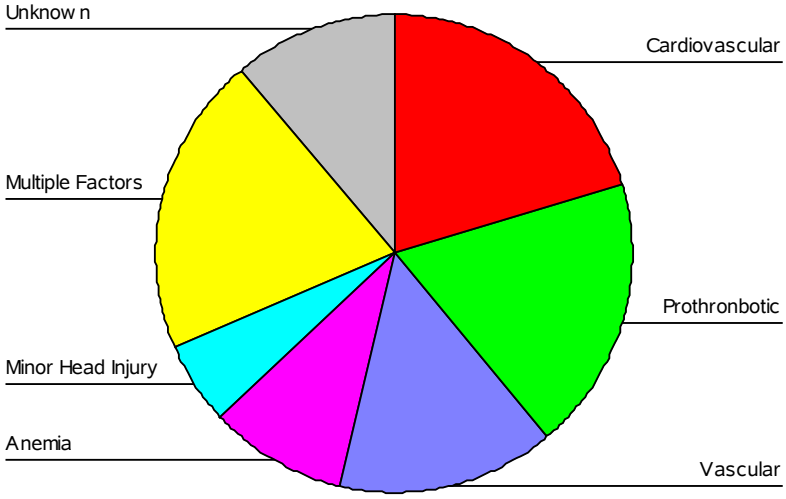
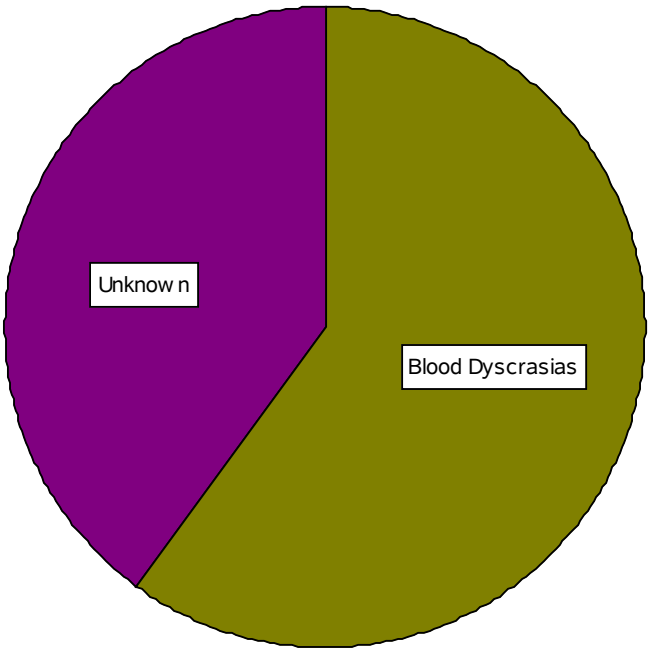


ETIOLOGY OF HEMORRHAGIC STROKE



DISCUSSION

1.- MEAN AGE AT ONSET

—The mean age at the onset of the present study is 4.4 yrs compared the studies mentioned below.

Study	Mean age of presentation
Ganesan et al (2003)	5
Delsing et al (2001)	4.3
Gabis et al (2002)	8.67
Jennifer et al (2007)	8.2
Chung et al (2004)	5.6
Simma et al (2007)	6
Present study	4.4 yrs

2.- SEX DISPARITY

—In the present study, the percentage of males among the 68 cases was 42%, in contrast with other studies mentioned below showing a male preponderance.

Study	Percentage of males
Ganesan et al (2003)	54%
Delsing et al (2001)	50%
Jennifer et al (2007)	53.3%
Chung et al (2004)	56%
Simma et al (2007)	60%
Present study	42%

3.- SIDE OF LESION

——Right sided hemiplegia is more common in the present study which correlates with the observation of Lee et al (2008) and Delsing et al (2001).

Study	Side of lesion
Lee et al (2008)	51% right
Delsing et al (2001)	59% right
Present study	52% right

4.- TIME LAG FOR FIRST MEDICAL CONTACT

——The average time lag from the onset of weakness to first medical contact in our study is 70 hrs. Gabis et al (2002) observed the same to be 28.5 hrs. The benefits of intravenous thrombolysis are lost beyond 3 hours. After this time, any benefit is overcome by an increasing incidence of symptomatic intracerebral hemorrhage. Hence majority of children are ineligible to receive thrombolytic therapy according to adult thrombolysis criteria.

Study	Time from clinical onset to medical contact
Gabis et al (2002)	28.5 hours
Present study	70 hrs

5.- FAMILY HISTORY

—Family history of stroke was obtained in 1.5% of the cases in the present study which correlates with the observation of Barreirinho et al (2003) and chung et al (2004) stating that a positive family history of stroke or myocardial infarction is not obtained in majority of the cases.

Study	Family history
Barreirinho et al (2003)	5% myocardial infarction
Chung et al (2004)	1% stroke
Present study	1.5% stroke

6.- HEMIPLEGIA WITH APHASIA

—Aphasia is an associated feature in 19% of cases in the present study. In contrast -

Delsing et al (2001) and Obama et al (1994) observed that higher percentage of the patients had aphasia whereas Jordan et al (2007) and chung et al (2004) observed that lesser percentage of the patients had aphasia.

Study	Aphasia
Delsing et al (2001)	25%
Obama et al (1994)	28.6%
Jordan et al (2007)	11%
Chung et al (2004)	10%
Present study	19%

7.- HEMIPLEGIA WITH SEIZURES

——In the study conducted by chung et al 2004 long-term neurologic deficits occurred among 41% of survivors, the only significant risk factor for long-term neurologic deficits was seizures at the initial presentation. Other factors, such as gender, age, other clinical features, stroke type, vascular territory, other causes, and recurrence of stroke, were all insignificant for both death and long-term deficits.

Study	Long-term neurologic deficits associated with seizures
Lee et al (2008)	29%
Delsing et al (2001)	19%
Steinlin et al	20%
Chung et al (2004)	52%
Jordan et al (2007	27%
Present study	41%

8.- CONSCIOUSNESS

——In the present study, 17.6% of cases presented with altered consciousness, 83.3% of whom had residual weakness. This observation correlates with that of Chung et al 2004 and Dusser et al who stated that decreased level of consciousness was a significant risk factor associated with high morbidity and mortality rates.

Study	Altered mental status
Delsing et al (2001)	16%
Chung et al (2004)	30%
Steinlin et al	35%
Jordan et al (2007)	6%
Present study	17.6%

9.- HEMIPLEGIA WITH FACIAL PALSY

—In the present study 39.7% of patients with hemiplegia had facial palsy in contrast with the study done by Obama et al (1994) who observed facial palsy in 62.9% of the cases.

Study	Facial paralysis
Obama et al (1994)	62.9%
Present study	39.7%

10.- NEUROIMAGING

—In the present study, all the patients enrolled had abnormalities in MRI which correlates with the study done by Liu GT et al (1990).

Study	MRI abnormalities
Liu GT et al (1990)	100%
Ganesan et al (2003)	91%
Jordan et al (2007)	80%
Present study	100%

11.- HEMORRHAGIC STROKE

—Hemorrhagic stroke as the cause of hemiplegia is around 7.3% in contrast with the studies mentioned below. The cause of hemorrhagic stroke as found in other studies is sickle cell anemia and moyamoya syndrome – both of which present at hemorrhagic stroke in children more than 15 yrs of age. Since the present study included children upto 12 yrs of age, the percentage of hemorrhagic stroke is significantly less.

Study	Hemorrhagic stroke
Chung et al (2004)	28%
Simma et al (2007)	27%
Lanthier et al (2000)	29%
Giroud et al (1997)	43%
Present study	7.3%

12.- EITIOLOGY OF ISCHEMIC STROKE

——In the present study 20.4% of the cases are due to cardioembolic cause, 18.5% are due to prothrombotic factors, 14.8% are due to arteriopathy, 14.7% are due to others, 11.2% are due to unknown factors and 20.4% are due to multiple risk factors.

Study	Cardio embolic	Pro thrombotic	Arteriopathy	Others	Unknown	Multiple risk factors
De Veber et al		38%				
Bonduel et al (1999)		30%				
Heller et al (1999)		31%				
Simma et al (2007)		50%				
Giroud et al (1997)	19				12.9	
Williams et al	15%	25%			36%	24%
Sreckovic et al (2004)	33.3%	11.1%	36.1%		19.4%	
Chabrier et al (2000)	12%	13%	53%		22%	
Lee et al (2008)	10%	13%	33%	34%	10%	22%
Delsing et al (2001)	19%	12.9%	26%	19.1%	23%	
Obama et al	17.1%				20%	

Study	Cardio embolic	Pro thrombotic	Arteriopathy	Others s	Unknown	Multiple risk factors
(1994)						
Chung et al (2004)	30%	26%	28%	4%	12%	
Lanthier et al (2000)						24%
Present study	20.4%	18.5%	14.8%	14.8%	11.1%	20.4%

13.- MULTIPLE RISK FACTORS

——In the present study, 16.1% of cases had multiple risk factors. 63.7% of children with multiple risk factors had poor outcome which correlates with the study done by Lanthier et al who ~~stated that~~stated that the coexistence of multiple stroke risk factors in children predicts poor outcome.

——In the study by Williams et al 24% had multiple risk factors, 22% in the study by Lee et al (2008) and 24% in the study by Lanthier et al (2000).

Multiple risk factors	Number	Good outcome	Poor outcome
Present study	11	4 (36.3%)	7 (63.7%)

13.- HOMOCYSTINURIA

——In the present study 4.4% of the patients had homocystinuria which is in contrast to the study by Beynum et al (1999) in which 18% had homocystinuria.

Study	Homocystinuria
Beynum et al (1999)	18%
Present study	4.4%

14.- PROTEIN S DEFICIENCY

——Protein S deficiency was observed in 10.2% of cases, which correlates with the observation of Usman et al (2007) and De Veber at al.

Study	Protein S deficiency
Usman et al (2007)	13.5%
De Veber at al	11.5%
Present study	10.2%

15.- PROTEIN C DEFICIENCY

——Protein C deficiency was observed in 2.9% of cases in contrast to the study by Usman et al (2007), Heller et al (1999) and De Veber at al.

Study	Protein C deficiency
Usman et al (2007)	5.4%
Heller et al (1999)	7%
De Veber at al	7%
Present study	2.9%

16.- SICKLE CELL ANEMIA

——The age of occurrence of first stroke in children with sickle cell anemia in the present study is before 6 yrs which correlates with the observation by Oliveira et al (2008).

Study	Sickle cell anemia age of presentation
Oliveira et al (2008)	<6 yrs
Present study	<6yrs

17.- OUTCOME

——In the present study, 60.2% had residual weakness which correlates with deVeber et al (2000).

——In contrast, Lanthier et al (2000), Chung et al (2004), Delsing et al (2001) observed that only around 30% of cases had residual weakness.

—In the present study, only 3% of cases died which correlates with the study of Obama et al (1994).

Study	Motor deficit	Death
Lanthier et al (2000)	36%	20%
Schoenberg et al	75%	16%
Obama et al (1994)	100%	2.9%
DeVeber et al (2000)	63%	
Simma et al (2007)	45%	0%
Chung et al (2004)	30%	18%
Jordan et al		16%
Lee et al (2008)		9%
Delsing et al (2001)	29%	13%
Present study	60.2%	3%

18.- RECURRENT STROKE

In the present study, 1 case (3%) with homocystinuria had recurrence of stroke on follow up. This correlates with the observation of Simma et al (2007). The incidence of stroke may also be related to the duration of follow up.

Study	Overall Recurrent stroke
Lee et al (2008)	16%
Lanthier et al (2000)	24%
Sreckovic et al (2004)	13.9%
Chabrier et al (2000)	20%
Simma et al (2007)	4%
Delsing et al (2001)	22%
Ganesan et al (2006)	41%
Fullerton et al (2007)	10%
Strater et al (2002)	6.6%
Lynch et al (2004)	33%
Becker et al (2002)	6.6%
Lanska et al (1991)	19%
Bonduel et al (2006)	1.1%
Present study	3%

SUMMARY

1. 68 children with hemiplegia (2 months to 12 years) were studied.

2. There was no significant difference in the incidence of hemiplegia between males and females (42% males vs 58% females).

3. There was no significant difference in the side of hemiplegia (52% right hemiplegia vs 48% left hemiplegia).

4. Past history of chicken pox was found in 4.4% of cases.

5. Aphasia was associated with 28.5% of cases with right sided weakness vs 9% of cases with left sided weakness.

6. Association of seizures with neurological outcome is not statistically significant (p=0.508). Among the patients who had seizures, 68% had poor residual motor weakness whereas 60% of cases who were seizure free had residual weakness.

7. Association of altered level of consciousness with poor neurological outcome is statistically not significant (p=0.195). 85.3% of cases who were drowsy at the onset and 80% of cases who were unconscious at the onset had residual weakness whereas 55% of patients who were alert at the onset had residual weakness.

8. Association of severity of neurological deficit with neurological outcome is statistically significant (p=0.031). 67.4% of patients with moderate weakness and 88.5% of cases with severe weakness had residual weakness whereas only 35.7% of cases with mild weakness had residual weakness.

9. MRI was abnormal in all patients (infarct in 83.8%, hemorrhage in 10.3% and space occupying lesion in 5.9%).

10. The observation of the etiology of hemiplegia revealed that 769.4% of cases were ischemic stroke, 107.3% were hemorrhagic stroke, 5.8% were due to space occupying lesions, 5.8% were due to infective etiology and 1.7% was due to metabolic cause.

11. The observation of the etiology of ischemic stroke revealed that 20.4% of cases had underlying cardiac disorder, either congenital or acquired followed by prothrombotic factors identified in 18.5% of cases, vascular etiology in 14.8%, miscellaneous causes in 14.7%, multiple risk factors in 20.4% and cause unknown in 11.2%.

12. Underlying cardiac disorder, either congenital or acquired was observed in 16% of cases and was the most common risk factor followed by prothrombotic factors in 14.7%, which was statistically significant (chi-square test - p=0.036).

13. The observation of the etiology of hemorrhagic stroke revealed that 60% of hemorrhagic stroke were due to blood dyscrasias and in 40% of cases, cause could not be identified.

14. Because of the high prevalence and importance of multiple risk factors, complete investigation, including hematological and metabolic studies and angiography, should be considered in every child with ischemic stroke, even when a cause is known.

CONCLUSION

From this study it is concluded that ischemic stroke is more common than hemorrhagic stroke in children between 2 months and 12 years. The most common cause of ischemic stroke is cardiovascular and that of hemorrhagic stroke is blood dyscrasias. Seizures and altered level of consciousness were not significantly associated with poor neurological outcome, whereas the severity of motor weakness at the onset is associated with poor neurological outcome. Presence of multiple risk factors is associated with poor neurological outcome. Because of the high prevalence and importance of multiple risk factors, a complete investigation, including hematological and metabolic studies and angiography, should be considered in every child with ischemic stroke, even when a cause is known. Similarly, hemorrhagic stroke is associated with poor neurological outcome. There are no proven or widely accepted strategies for acute management or diagnostic evaluation of intra parenchymal hemorrhage in childhood, and limited data exist on the risks vs benefits of existing treatment approaches. There is a paucity of literature to guide physicians who care for children with hemorrhagic stroke. Additional work is required in hemorrhagic, as well as arterial ischemic stroke in childhood. Randomized controlled trials of intervention will be essential.

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Wraige E, Hajat C, Jan W, et al. Ischaemic stroke subtypes in children and adults. Dev Med Child Neurol 2003;45:229.

~~PROFORMA~~

~~Name~~

~~Age~~

~~Sex~~

~~Unit~~

~~IP NO~~

~~Date of admission and discharge~~

~~Presenting complaints~~

~~Sudden weakness of one side of body~~

~~Onset~~

~~Type~~

~~Duration~~

~~Side of lesion~~

~~Speech~~

Vision

Seizures

Fever

Severe headache and vomiting

Loss of consciousness

Past history

Family history

Bleeding disorder or

Young stroke (in parents, uncle and grand parents)

General examination

Neurological examination

Investigations

I. For all patients

CSF analysis

Imaging : MRI scan

II. For patients presenting with infarct in typical vascular distribution:

Cardiac evaluation

ECG

- ~~Echocardiogram~~
- ~~Carotid doppler~~
- ~~Blood tests~~
- ~~Complete blood count~~
- ~~Erythrocyte sedimentation rate~~
- ~~Protein C~~
- ~~Protein S~~
- ~~Antiphospholipid antibodies~~
- ~~Serum homocysteine~~
- ~~Lipid profile~~
- ~~III. For patients presenting with infarct with non vascular distribution~~
- ~~Serum lactate & pyruvate~~
- ~~IV. For patients with hemorrhage~~
- ~~Platelet count~~
- ~~Coagulation study~~
- ~~Bleeding time~~
- ~~Clotting time~~

~~Prothrombin time~~

~~APTT~~

~~Final diagnosis~~

~~Treatment~~

~~Follow up : periodically every 3 months for 1-2 years~~

~~_____~~

ANNEXURE - I

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ANNEXURE – II

PROFORMA

1.	Name :		
2.	I.P.No.:		
3.	Unit :		
4.	Date of admission:		
5.	Date of Discharge:		
6.	Age in months:		
7.	Sex:	1.	Male
		2.	Female
8.	Address:		
9.	Phone No.		
10.	Area:	1.	Urban
		2.	Rural
11.	Maternal Education	1.	Illiterate
		2.	Primary Schooling
		3.	Secondary schooling
		4.	Graduation
12.	Father's Occupation:	1.	Cooly
		2.	Clerical Job/Teacher
		3.	Self-employed
		4.	High Class

PRESENTING COMPLAINTS:

13.	Motor Weakness:	1.	One side weakness
		2.	One side weakness following seizures
		3.	Starts with loss of consciousness
		4.	Transient ischemic attacks
		5.	Evolving weakness

Figure : 1 Arterial Supply of Brain

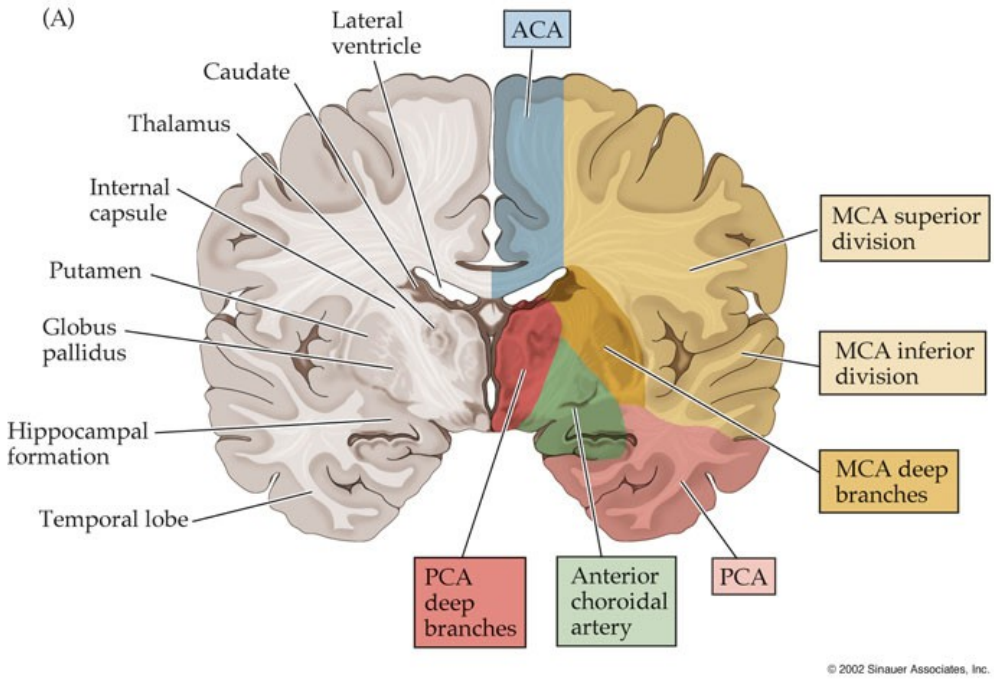
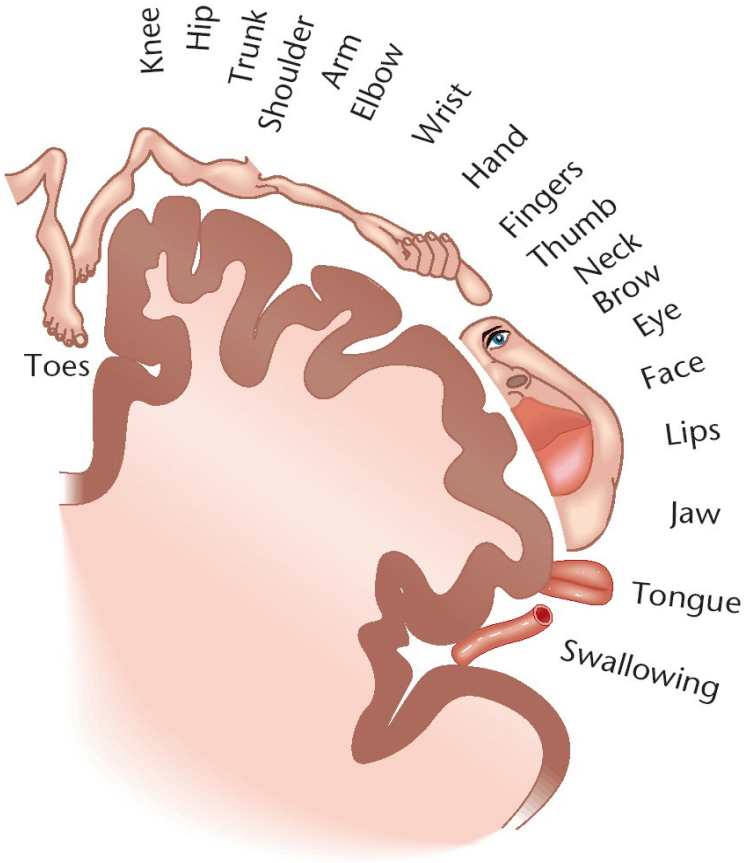


Figure : 2 Motor Homonculus



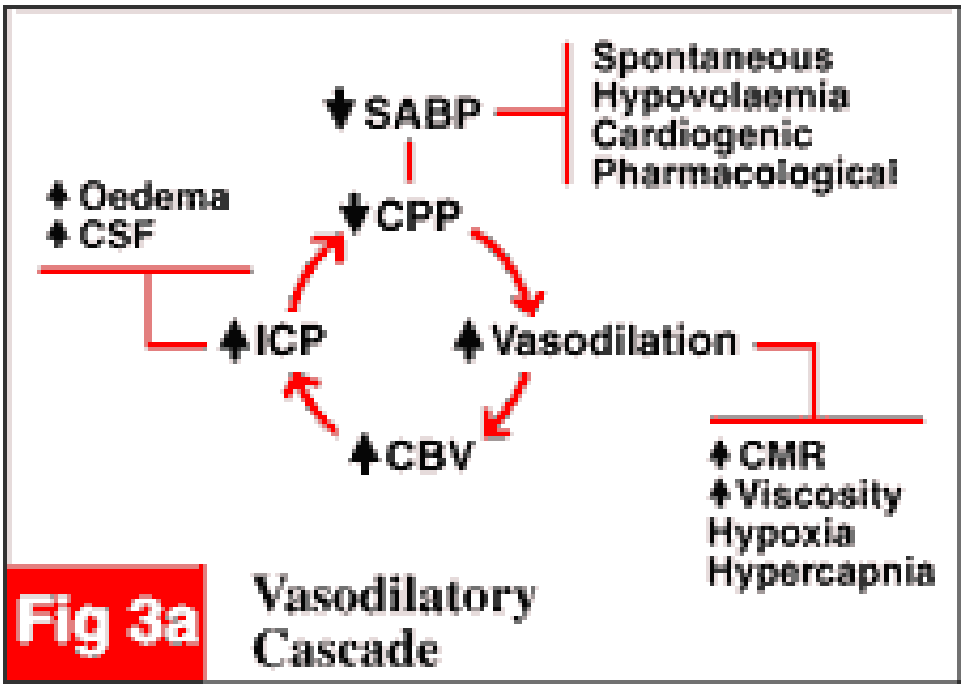


Fig 3a Vasodilatory Cascade

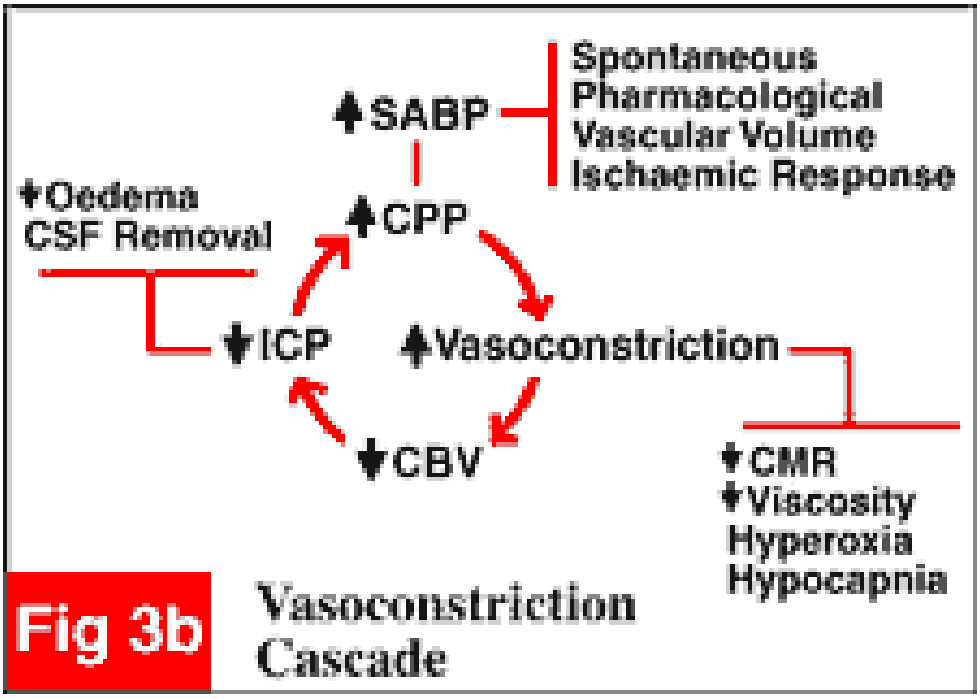
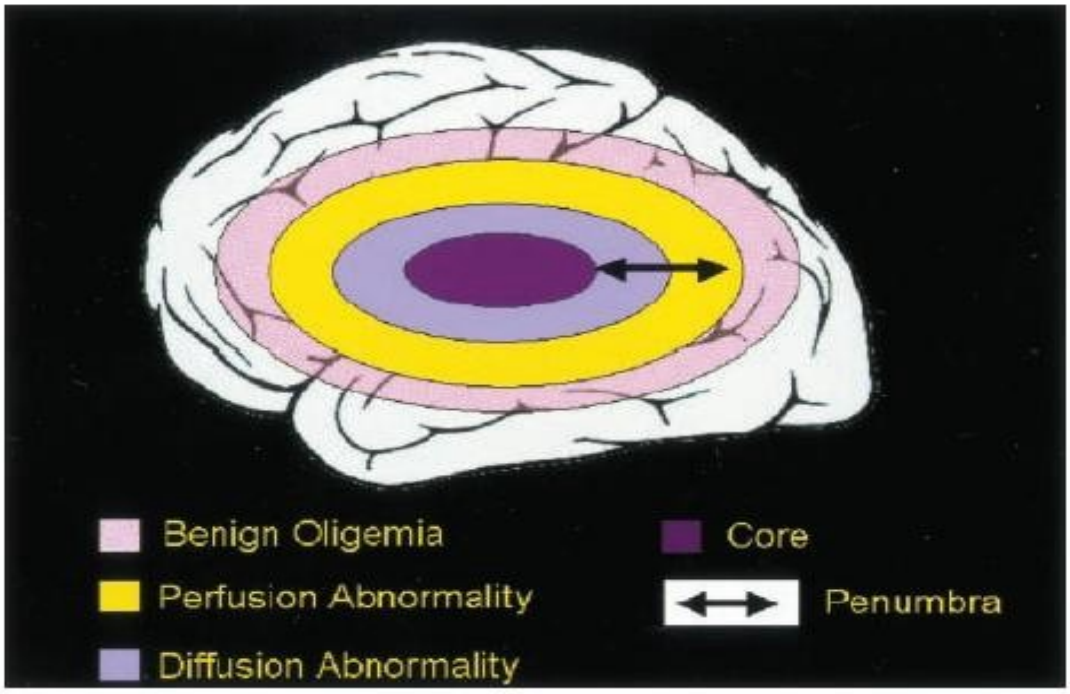
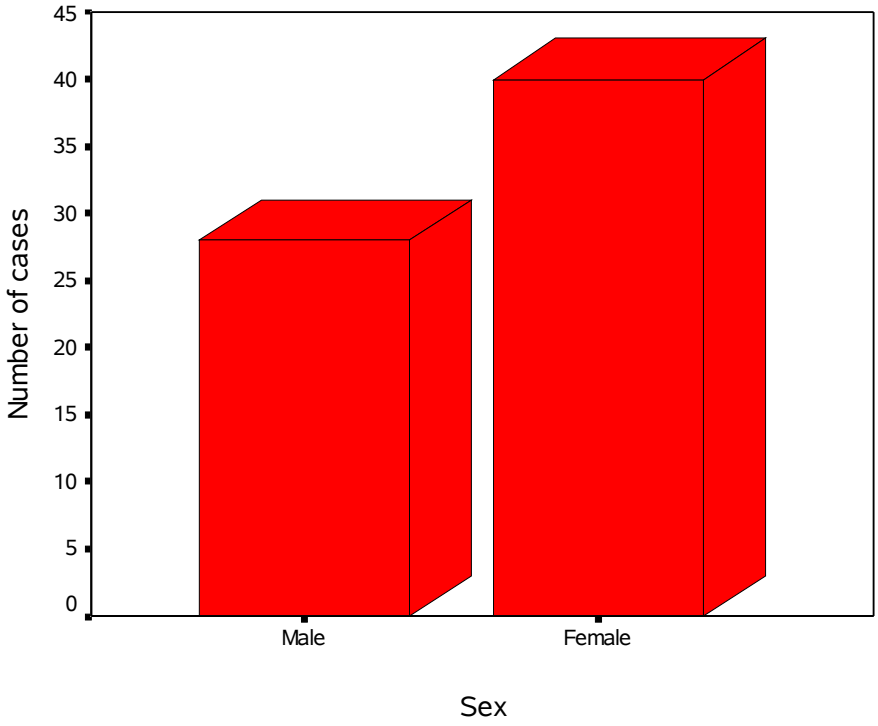


Fig 3b Vasoconstriction Cascade

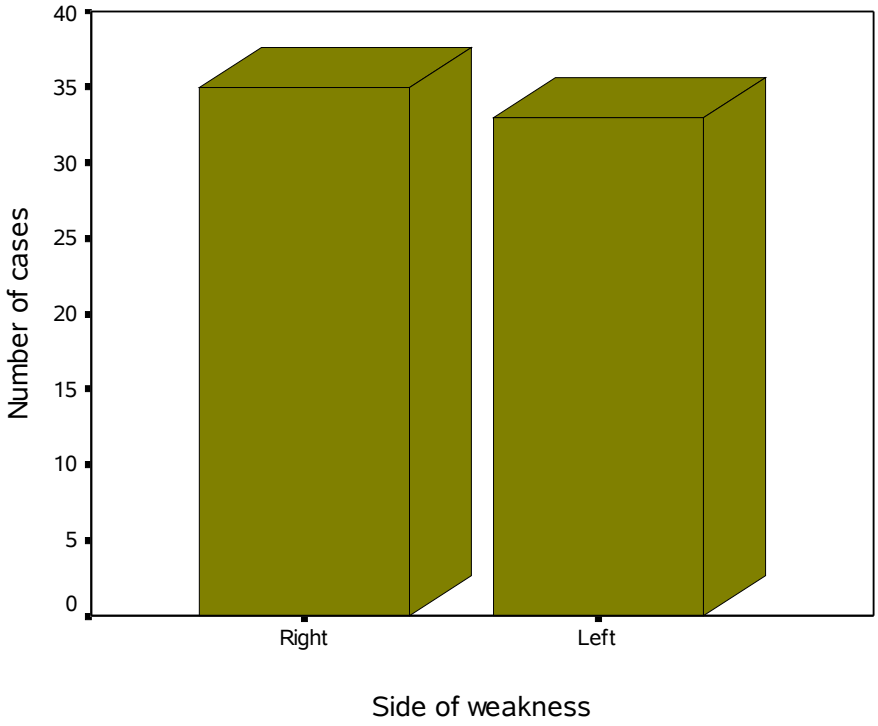
Figure : 4 Ischemic penumbra



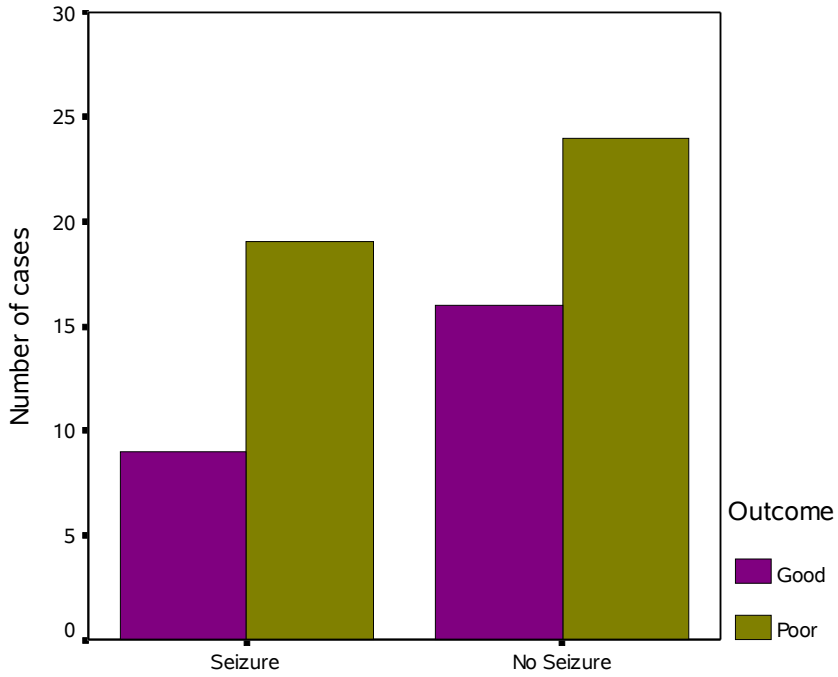
Picture 1: SEX DISTRIBUTION



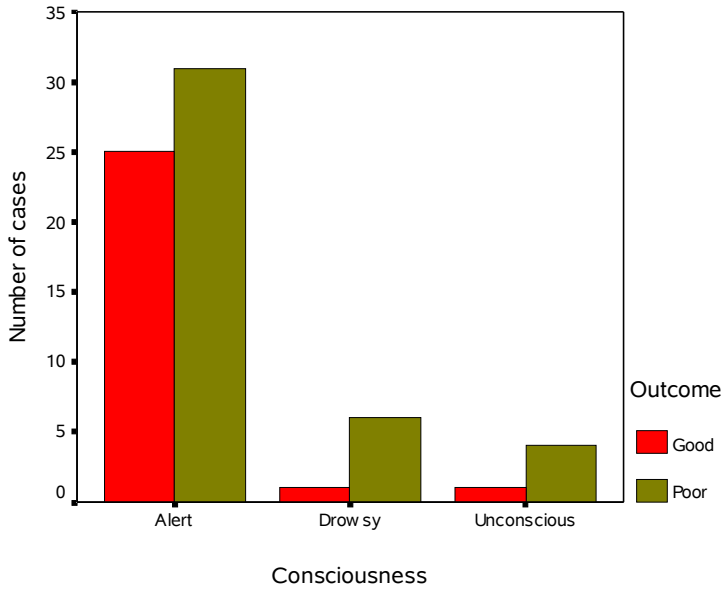
Picture 2 : SIDE OF WEAKNESS



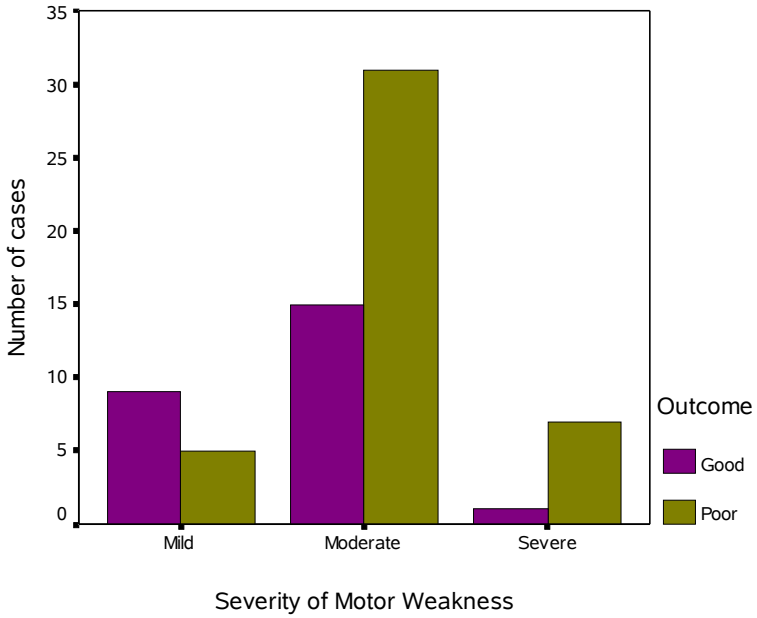
Picture 3 : OUTCOME WITH RELATION TO SEIZURES AT ONSET



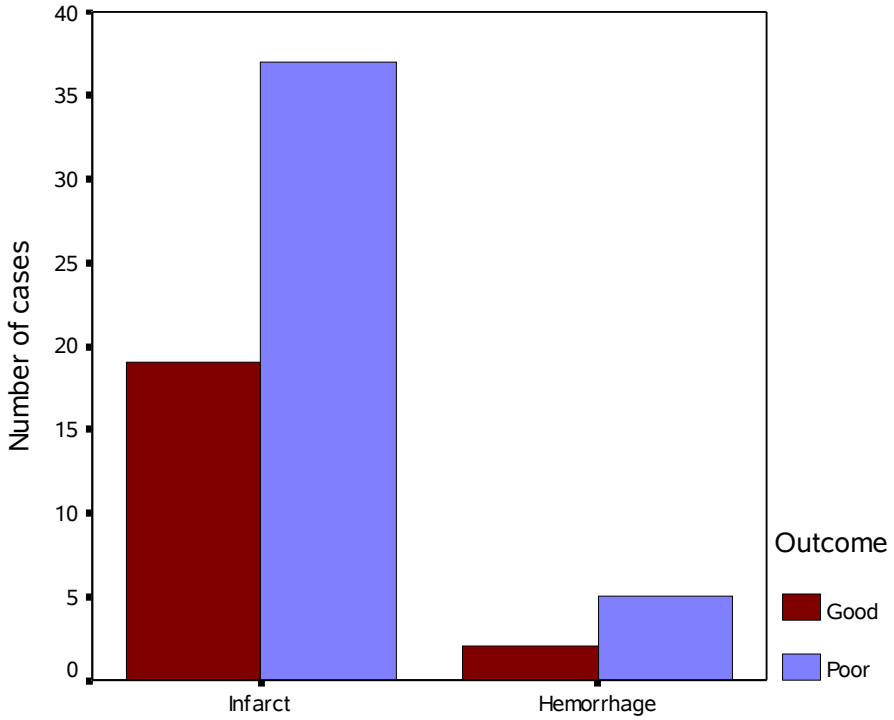
Picture 4 : OUTCOME WITH RELATION TO CONSCIOUSNESS AT ONSET



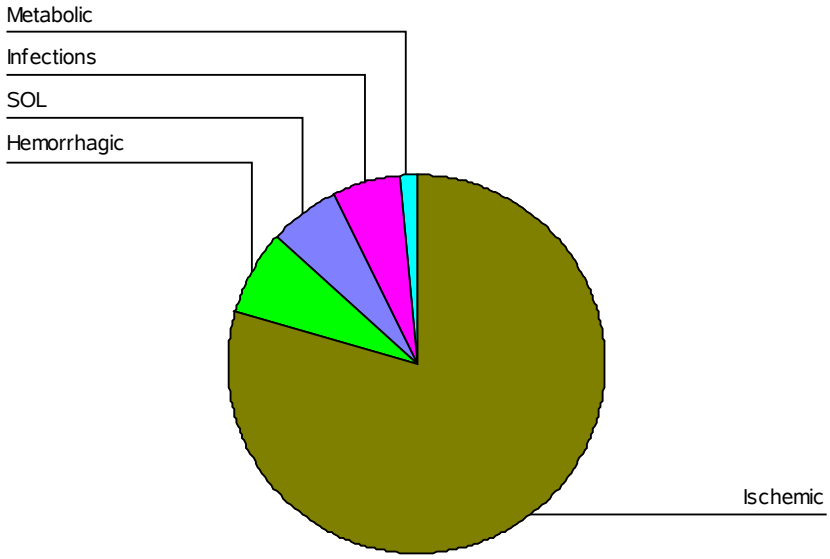
Picture 5 : OUTCOME WITH RELATION TO THE SEVERITY OF WEAKNESS AT ONSET



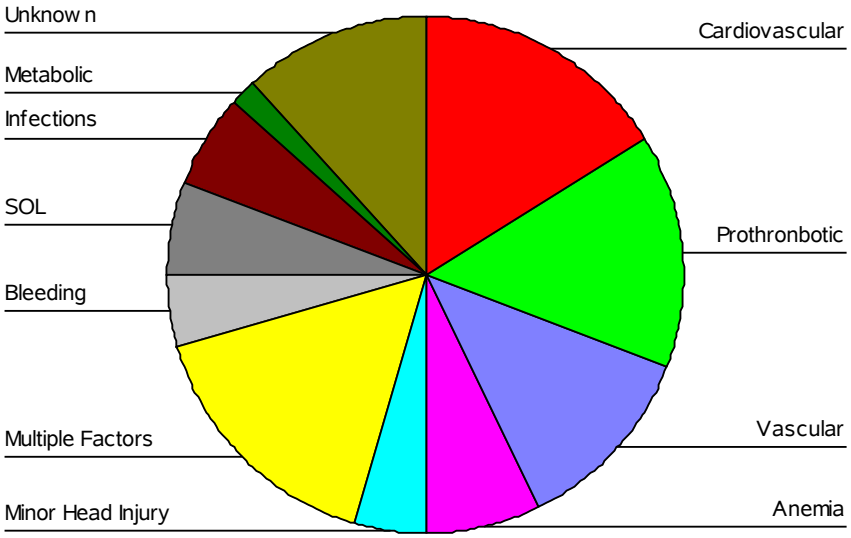
Picture 6 : OUTCOME OF ISCHEMIC VS HEMORRHAGIC INFARCT



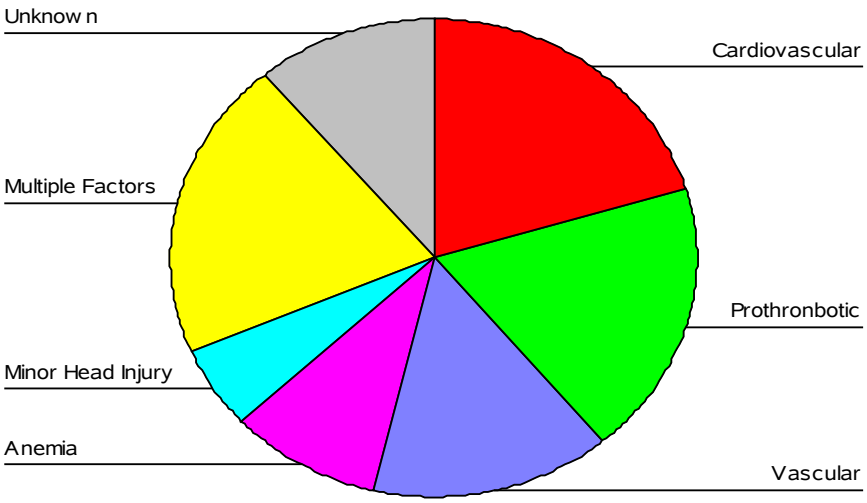
Picture 7 : ETIOLGY OF HEMIPLEGIA



Picture 8 : ETIOLOGY OF HEMIPLEGIA



Picture 9 : ETIOLOGY OF ISCHEMIC STROKE



Picture 10 : ETIOLOGY OF HEMORRHAGIC STROKE